DATE 6-13-07 APPLICATION NUMBER 08/416242

DOC CODE TERM-REQ DOC DATE 4-2-07

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CONTRACTOR: THE ATTACHED FILE/DOCUMENT MUST BE INDEXED AND SCANNED INTO IFW WITHIN **8** WORK HOURS; UPLOADING OF THE SCANNED IMAGES SHOULD OCCUR NO LATER THAN **16** WORK HOURS FOLLOWING RECEIPT OF THIS REQUEST

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CASE 4-19919/A

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

EV706064065US
Express Mail Label Number

March 30, 2007
Date of Deposit

#15

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE U.S. PATENT NO. 5,559,111 B1

ISSUED: SEPTEMBER 24, 1996

INVENTORS: RICHARD GÖSCHKE, JÜRGEN K. MAIBAUM, WALTER SCHILLING, STEFAN STUTZ, PASCAL RIGOLLIER, YASUCHIKA YAMAGUCHI, NISSIM CLAUDE COHEN AND PETER HEROLD

FOR: δ-AMINO-γ-HYDROXY-ω-ARYL-ALKANOIC-ACID AMIDES

MS Patent Ext.
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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APR 02 2007
OFFICE OF PETITIONS

TRANSMITTAL LETTER FOR PATENT TERM EXTENSION APPLICATION

Sir:

Enclosed in triplicate is an application for the extension of U.S. Patent No. 5,559,111 under 35 U.S.C. §156.

The Commissioner is hereby authorized to charge the Application Fee of $1,120.00 prescribed by 37 C.F.R. §1.20(j)(1), as well as any additional fees which may be necessitated in connection with the filing of this Application for Patent Term Extension, to Applicant's Deposit Account No. 19-0134 in the name of Novartis. Two additional copies of this transmittal letter are being submitted for charging purposes.

Respectfully submitted,

Gregory Ferraro

Gregory D. Ferraro
Attorney for Applicant
Reg. No. 36,134

Novartis
Corporate Intellectual Property
One Health Plaza, Building 104
East Hanover, NJ 07936-1080
(862) 778-7831
Date: March 29, 2007

Encl.: Patent Term Extension Application including Appendices A-F in triplicate
Two additional copies of this transmittal letter
Postcard

CASE 4-19919/A

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

EV706064065US
Express Mail Label Number

3/30/07
Date of Deposit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE U.S. PATENT NO. 5,559,111

ISSUED: September 24, 1996

INVENTORS: RICHARD GÖSCHKE, JÜRGEN K. MAIBAUM, WALTER SCHILLING, STEFAN STUTZ, PASCAL RIGOLLIER, YASUCHIKA YAMAGUCHI, NISSIM CLAUDE COHEN AND PETER HEROLD

FOR: δ-AMINO-γ-HYDROXY-ω-ARYL-ALKANOIC-ACID AMIDES

MS Patent Ext.
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PATENT TERM EXTENSION APPLICATION UNDER 35 U.S.C.§156

Sir:

Pursuant to 35 U.S.C.§156 and 37 C.F.R.§1.710 *et seq.*, Novartis Corporation ("Applicant"), a Corporation of the State of New York, hereby requests an extension of the patent term, due to regulatory review, of U.S. Patent No. 5,559,111, which was granted on September 24, 1996.

Applicant asserts that it is the owner of the entire right, title and interest in U.S. Patent No. 5,559,111 by virtue of an assignment from the inventors, Richard Göschke, Jürgen K. Maibaum, Walter Schilling, Stefan Stutz, Pascal Rigollier, Yasuchika Yamaguchi, Nissim C. Cohen and Peter Herold to Ciba-Geigy Corporation, which later changed its name to Novartis Corporation. The assignment from the inventors was recorded in the United States Patent and Trademark Office on April 29, 1996 at Reel 007916, Frame 0856 and the change of name from Ciba-Geigy Corporation to Novartis Corporation was recorded in the U.S. Patent and Trademark Office on August 22, 2000 at Reel 011089, Frame 0648. Copies of each of these documents evidencing that title to U.S. Patent No. 5,559,111 is vested in Novartis Corporation are attached hereto as Appendix A.

An originally executed Power of Attorney evidencing that the undersigned is an attorney authorized to act on behalf of Novartis Corporation is attached hereto as Appendix B. Although not dated this Power of Attorney was signed on March 28, 2007

In accordance with 35 U.S.C.§156 and 37 C.F.R.§1.740, Applicant provides the following information in support of its request for a patent term extension. The following sections are set forth in the order by which they are required by 37 C.F.R.§1.740.

(1) Identification of the Approved Product

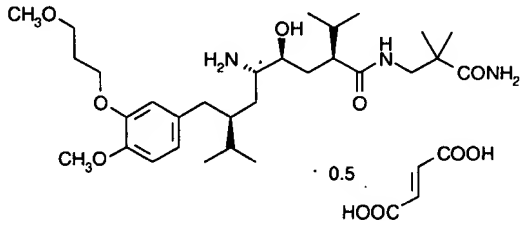
(a) Chemical name: 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethyl-ethyl)-amide hemifumarate; also known as (2S, 4S, 5S, 7S)-N-(2-Carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]-octanamide hemifumarate.

(b) Trademark: TEKTURNA®

(c) USAN Name: Aliskiren hemifumarate

(d) Code: SPP 100

(e) Chemical Structure:



2. Identification of the Federal Statute under which Regulatory Review Occurred

The approved product was subject to regulatory review under the Federal Food, Drug and Cosmetic Act, Section 505 (21 U.S.C.§355).

3. The Date of Permission for Commercial Marketing

The approved product received permission for commercial marketing under Section 505(c) of the Federal Food, Drug and Cosmetic Act (21 U.S.C.§355(c)) on March 5, 2007. A copy of the FDA approval letter, with accompanying labeling, is attached hereto as Appendix C.

4. Active Ingredient Statement

The sole active ingredient in Tekturna® is aliskiren. Aliskiren, or any salt thereof, has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum Toxin Act prior to the approval of NDA 21-985 by the United States Food and Drug Administration on March 5, 2007.

5. Statement of Timely Filing

The last day on which this application could be submitted is May 4, 2007, which is 60 days after the approval of NDA 21-985 on March 5, 2007. This application is timely filed on or prior to May 4, 2007.

6. Identification of Patent for which Extension is Sought

This application seeks to extend the term of U.S. Patent No. 5,559,111, which issued September 24, 1996 to Richard Göschke, Jürgen K. Maibaum, Walter Schilling, Stefan Stutz, Pascal Rigollier, Yasuchika Yamaguchi, Nissim C. Cohen and Peter Herold, the term of which would otherwise expire on April 4, 2015.

7. Patent Copy

A complete copy of U.S. Patent No. 5,559,111, identified in paragraph 6 above, is attached as Appendix D.

8. Post-Issuance Activity Statement

No Disclaimer, Certificate of Correction, Reexamination certificate or Reissue have been issued or requested with respect to U.S. Patent No. 5,559,111. Two maintenance fees have become due since the patent has issued and both have been paid in a timely manner. A copy of the maintenance fee statements received by the United States Patent & Trademark Office

indicating that the respective maintenance fees were timely paid, are attached hereto as Appendix E.

9. Statement Showing How the Claims of the Patent for which Extension is Sought Cover the Approved Product

Claims 1, 2, 3, 4, 5, and 19 of U.S. Patent No. 5,559,111 claim a compound or compounds which include the approved product, aliskiren hemifumarate. Claim 8 claims a composition and Claim 9 claims a method.

Claim 19 claims aliskiren or any salt thereof, by its chemical name, which is 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethyl-ethyl)-amide.

Claim 19 reads as follows:

19. A compound according to claim I being 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethyl-ethyl)amide or a salt thereof.

Claim 9 claims a method of treating many diseases, amongst them, hypertension by administering to a warm-blooded organism in need of such treatment a therapeutically effective amount of a compound according to claim 1 in the free form or in the form of a pharmaceutically acceptable salt with a compound or compounds which include the approved product, aliskiren hemifumarate.

Claim 9 reads as follows:

9. A method of treating hypertension, congestive heart failure, cardiac hypertrophy, cardiac fibrosis, cardiomyopathy postinfarction, nephropathy, vasculopathy, neuropathy, restenosis following angioplasty, raised intra-ocular pressure, glaucoma, abnormal vascular growth, hyperaldosteronism or anxiety states, characterized in that a therapeutically effective amount of a compound according to claim 1 in the free form or in the form of a pharmaceutically acceptable salt is administered to a warm-blooded organism in need of such treatment.

Aliskiren hemifumarate is the compound of claim 1 wherein R_1 is hydrogen, R_2 is lower alkoxy-lower alkoxy, R_3 is lower alkoxy, R_4 is hydrogen, X is methylene, R_5 is lower alkyl, R_6 is

unsubstituted amino, R_7 is lower alkyl, and R_8 is amidated carboxy-lower alkyl, which compound is in hemifumarate salt form.

10. Statement of the Relevant Dates to Determine the Regulatory Review Period

The relevant dates and information pursuant to 35 U.S.C.§156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(i) The patent for which extension of the term thereof is sought claims a human drug product. The human drug product is aliskiren hemifumarate.

(A) An Investigational New Drug Application for aliskiren was submitted on July 19, 2001, was received by the Department of Health and Human Services on July 23, 2001, was assigned IND No. 62,976 , and became effective on August 22, 2001. The original IND was filed for hypertension. A copy of the IND letter from the FDA is attached as Appendix F.

(B) A New Drug Application for Tekturna® was received by the Department of Health and Human Services on February 13, 2006 and granted NDA No. 21-985.

(C) NDA No. 21-985 was approved on March 5, 2007.

11. Brief Description of Activities Undertaken During the Regulatory Review Period

As a brief description of the activities undertaken during the applicable regulatory review period, attached hereto as Appendix G is a chronology of the major communications between the U.S. Food and Drug Administration and the Applicant in IND No. 62,976 and NDA No. 21-985.

12. Opinion of Eligibility for Extension

Applicant is of the opinion that U.S. Patent No. 5,559,111 is eligible for extension under 35 U.S.C.§156 and 37 C.F.R.§1.720 because it satisfies all of the requirements for such extension as follows:

(a) 35 U.S.C.§156(a) and 37 C.F.R.§1.720(a)

U.S. Patent No. 5,559,111 claims aliskiren hemifumarate, the active ingredient of a human drug product, pharmaceutical compositions thereof and a method of use thereof.

(b) 35 U.S.C.§156(a)(1) and 37 C.F.R.§1.720(g)

The term of U.S. Patent No. 5,559,111 (expiring April 4, 2015) has not expired before the submission of this application.

(c) 35 U.S.C.§156(a)(2) and 37 C.F.R.§1.720(b)

The term of U.S. Patent No. 5,559,111 has never been extended.

(d) 35 U.S.C.§156(a)(3) and 37 C.F.R.§1.720(c)

The application for extension of the term of U.S. Patent No. 5,559,111 is submitted by the authorized attorney of the owner of record thereof in accordance with the requirements of 35 U.S.C.§156(d) and 37 C.F.R.§1.740.

(e) 35 U.S.C.§156(a)(4) and 37 C.F.R.§1.720(d)

The approved product, Tekturna®, has been subjected to a regulatory review period before its commercial marketing or use.

(f) 37 C.F.R.§1.720(h)

No other patent has been extended for the same regulatory review period for the approved product, Tekturna®.

(g) 35 U.S.C.§156(a)(5)(A) and 37 C.F.R.§1.720(e)(1)

The permission for the commercial marketing or use of the approved product, Tekturna® is the first received permission for commercial marketing or use of Tekturna® under the provision of law under which the applicable regulatory review occurred.

13. **Length of extension claimed under 37 C.F.R.§1.740(a)(12)**

The length of extension of the patent term of U.S. Patent No. 5,559,111 requested by Applicant is 1204 days, which length was calculated in accordance with 37 C.F.R.§1.775 as follows:

(a) The regulatory review period under 35 U.S.C.§156(g)(1)(B)(i), began on August 22, 2001 (the effective date of the IND) and ended on March 5, 2007, amounting to a total of 2022 days which is the sum of (i) and (ii) below:

(i) The period of review under 35 U.S.C.§156(g)(1)(B)(i), the "Testing Period," began on August 22, 2001 and ended on February 13, 2006 which is 1,637 days;

(ii) The period for review under 35 U.S.C.§156(g)(1)(B)(ii), the "Application Period," began on February 13, 2006 and ended on March 5, 2007, which is 386 days;

(b) The regulatory review period upon which the period for extension is calculated is the entire regulatory review period as determined in subparagraph (13)(a) above (2022 days) less:

(i) The number of days in the regulatory review period which were on or before the date on which the patent issued (September 24, 1996), i.e., zero days, and

(ii) The number of days during which the Applicant did not act with due diligence, i.e., zero days, and

(iii) One-half of the number of days remaining in the period in subparagraph (13)(a)(i) after subtracting the number of days in subparagraphs (13)(b)(i) and (13)(b)(ii), which is one-half of (1637 - [0 + 0]) or 818 days;

which results in a period of 2022 -[0 + 0 + 818 days] = 1204 days.

(c) The number of days as determined in subparagraph (13)(b), when added to the original term (April 4, 2015), would result in the date of July 21, 2018.

(d) Fourteen (14) years when added to the date of the NDA Approval Letter (March 5, 2007) would result in the date of March 5, 2021.

(e) The earlier date as determined by subparagraphs (13)(c) and (13)(d) is July 21, 2018.

(f) Since the original patent was issued after September 24, 1984, the extension otherwise obtainable is limited to not more than five (5) years. Five years, when added to the original expiration of U.S. Patent No. 5,559,111 (April 4, 2015), results in the date April 4, 2020.

(g) The earlier date as determined in subparagraphs (13)(e) and (13)(f) is July 21, 2018.

14. Duty of Disclosure Acknowledgement Under 37 C.F.R.§1.740(a)(13)

Applicant acknowledges a duty to disclose to the Commissioner of Patent and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

15. Fee Charge Required by 37 C.F.R.§1.740(a)(14)

The prescribed fee for receiving and acting upon this application is to be charged to Applicant's Deposit Account No. 19-0134 as authorized in the attached transmittal letter, submitted in triplicate.

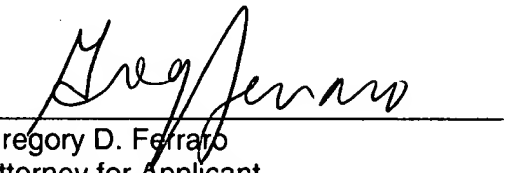
16. **Correspondence Address Required by 37 C.F.R.§1.740(a)(15)**

All correspondence relating to this application for patent term extension should be addressed to:

Novartis
Corporate Intellectual Property
One Health Plaza, Bldg. 104
East Hanover, NJ 07936-1080

The instant application, including its attachments and supporting papers, is being submitted as one original and two copies thereof in accordance with 37 C.F.R.§1.740(b).

Respectfully submitted,



Novartis
Corporate Intellectual Property
One Health Plaza, Building 104
East Hanover, NJ 07936-1080

Gregory D. Ferraro
Attorney for Applicant
Reg. No. 36,134
(862) 778-7831

Date: March 29, 2007

APPENDIX A

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

JULY 24, 1996

PTAS

100187600A

CIBA-GEIGY CORPORATION
MICHAEL W. GLYNN
PATENT DEPARTMENT
520 WHITE PLAINS ROAD - P.O. BOX 2005
TARRYTOWN, NEW YORK 10591-9005

RECEIVED
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PATENT DEPARTMENT
ANDREA LAMBERTI

UNITED STATES PATENT AND TRADEMARK OFFICE
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RECORDATION DATE: 04/29/1996

REEL/FRAME: 7916/0856
NUMBER OF PAGES: 2

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR: GOSCHKE, RICHARD	DOC DATE: 02/28/1995
ASSIGNOR: MAIBAUM, JURGEN KLAUS	DOC DATE: 02/28/1995
ASSIGNOR: SCHILLING, WALTER	DOC DATE: 02/28/1995
ASSIGNOR: STUTZ, STEFAN	DOC DATE: 02/28/1995
ASSIGNOR: RIGOLLIER, PASCAL	DOC DATE: 02/28/1995
ASSIGNOR: YAMAGUCHI, YASUCHIKA	DOC DATE: 02/28/1995
ASSIGNOR: COHEN, NISSIM CLAUDE	DOC DATE: 02/28/1995

Copy Sent to Basle
8/5/96
L.C.

ASSIGNOR:
HEROLD, PETER DOC DATE: 02/28/1995

ASSIGNEE:
CIBA-GEIGY CORPORATION
520 WHITE PLAINS ROAD - P.O. BOX 2005
PATENT DEPARTMENT
TARRYTOWN, NEW YORK 10591-9005

SERIAL NUMBER: 08416242 FILING DATE: 04/04/1995
PATENT NUMBER: ISSUE DATE:

JERYL MCDOWELL, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

FORM PTO-1595
(Rev. 6 3)
OMB No. 0651-0011 (exp. 4/94)

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05-07-19

100187600

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

To the Honorable Commissioner of Patents and Trader

uments or copy thereof.

1. Name of conveying party(ies):
Richard Goschke, Jurgen Klaus Maibaum, Walter Schilling, Stefan Stutz, Pascal Rigollier, Yasuchika Yamaguchi, Nissim Claude Cohen and Peter Herold
Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies)
Name: Ciba-Geigy Corporation
Internal Address: Patent Department

Street Address: 520 White Plains Road
P.O. Box 2005
City: Tarrytown State: NY ZIP: 10591-9005
Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:
☒ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other _____
Execution Date: February 28, 1995

4. Application number(s) or patent number(s):
If this document is being filed together with a new application, the execution date of the application is: _____

A. Patent Application No.(s)
08/416,242 filed 4-4-95

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:
Name: Michael W. Glynn
Internal Address: Ciba-Geigy Corporation
Patent Department

Street Address: 520 White Plains Rd
P.O. Box 2005
City: Tarrytown State: NY ZIP: 10591-9005

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41).....$ 40
☐ Enclosed
☒ Authorized to be charged to deposit account and any other additional fees required.

8. Deposit account number:
07-0590
(Attach duplicate copy of this page if paying by deposit account)

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9. Statement and signature.
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Marla J. Mathias — Name of Person Signing
Mark J. Mathias — Signature
4/24/96 — Date

*certificate of mailing on reverse

Total number of pages including cover sheet, attachments, and document: 2

Mail documents to be recorded with required cover sheet information to:
Commissioner of Patents & Trademarks, Box Assignments
Washington, D.C. 20231

US Case **4-19919/A**

ASSIGNMENT

I (We)
Richard Göschke of 4103 Bottmingen, Switzerland,
Jürgen Klaus Maibaum of 79576 Weil-Haltingen, Germany,
Walter Schilling of 4204 Himmelried, Switzerland,
Stefan Stutz of 4053 Basle, Switzerland,
Pascal Rigollier of 68510 Sierentz, France,
Yasuchika Yamaguchi of 4053 Basle, Switzerland,
Nissim Claude Cohen of 68300 Village-Neuf, France and
Peter Herold of 4144 Arlesheim, Switzerland

for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to CIBA-GEIGY Corporation, a New York corporation, of 444 Saw Mill River Road, Ardsley, New York, 10502, U.S.A.,its successors, assigns and legal representatives, all our right, title and interest, in and for the United States of America, in and to the

Novel delta-amino-gamma-hydroxy-omega-aryl-alkanoic acid amides

invented by us and described in the application for United States Letters Patent therefor, executed on even date herewith, and all United States Letters Patent which may be granted therefor, and all divisions, reissues, continuations and extensions thereof, the said interest being the entire ownership of the said Letters Patent when granted, to be held and enjoyed by the said CIBA-GEIGY Corporation, its successors, assigns or other legal representatives, to the full end of the term for which said Letters Patent may be granted, as fully and entirely as the same would have been held and enjoyed by us if this assignment and sale had not been made;

And we hereby authorize and request the Commissioner of Patents and Trademarks to issue said Letters Patent to the said CIBA-GEIGY Corporation.

Signed on February 28, 1995

Richard Göschke
Jürgen Maibaum
Walter Schilling
Stefan Stutz
Pascal Rigollier
Yasuchika Yamaguchi
N. C. Cohen
Peter Herold

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

NOVEMBER 14, 2000

PTAS

101484946A

NOVARTIS CORPORATION
THOMAS HOXIE
564 MORRIS AVENUE
SUMMIT, NJ 07901-1027

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PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 08/22/2000

REEL/FRAME: 011089/0648
NUMBER OF PAGES: 5

BRIEF: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
CIBA-GEIGY CORPORATION

DOC DATE: 06/12/1997

ASSIGNEE:
NOVARTIS CORPORATION
608 FIFTH AVENUE
NEW YORK, NEW YORK 10020

OK SERIAL NUMBER: 29002441
PATENT NUMBER: D352107

FILING DATE: 12/10/1992
ISSUE DATE: 11/01/1994

OK SERIAL NUMBER: 06366792
PATENT NUMBER: 4409212

FILING DATE: 04/09/1982
ISSUE DATE: 10/11/1983

OK SERIAL NUMBER: 06426424
PATENT NUMBER: 4424221

FILING DATE: 09/28/1982
ISSUE DATE: 01/03/1984

OK SERIAL NUMBER: 06382972
PATENT NUMBER: 4444775

FILING DATE: 06/01/1982
ISSUE DATE: 04/24/1984

SERIAL NUMBER: 06426011 PATENT NUMBER: 4459298	FILING DATE: 09/28/1982 ISSUE DATE: 07/10/1984
SERIAL NUMBER: 06437420 PATENT NUMBER: 4478842	FILING DATE: 11/01/1982 ISSUE DATE: 10/23/1984
SERIAL NUMBER: 06434094 PATENT NUMBER: 4512987	FILING DATE: 10/13/1982 ISSUE DATE: 04/23/1985
SERIAL NUMBER: 06559861 PATENT NUMBER: 4559174	FILING DATE: 12/12/1983 ISSUE DATE: 12/17/1985
SERIAL NUMBER: 06584057 PATENT NUMBER: 4579683	FILING DATE: 02/27/1984 ISSUE DATE: 04/01/1986
SERIAL NUMBER: 06742680 PATENT NUMBER: 4590292	FILING DATE: 06/10/1985 ISSUE DATE: 05/20/1986
SERIAL NUMBER: 06746602 PATENT NUMBER: 4602014	FILING DATE: 06/19/1985 ISSUE DATE: 07/22/1986
SERIAL NUMBER: 06692255 PATENT NUMBER: 4649149	FILING DATE: 01/17/1985 ISSUE DATE: 03/10/1987
SERIAL NUMBER: 06621302 PATENT NUMBER: 4678800	FILING DATE: 06/15/1984 ISSUE DATE: 07/07/1987
SERIAL NUMBER: 06848661 PATENT NUMBER: 4692469	FILING DATE: 04/04/1986 ISSUE DATE: 09/08/1987
SERIAL NUMBER: 06780711 PATENT NUMBER: 4721787	FILING DATE: 09/26/1985 ISSUE DATE: 01/26/1988
SERIAL NUMBER: 06837489 PATENT NUMBER: 4749713	FILING DATE: 03/07/1986 ISSUE DATE: 06/07/1988
SERIAL NUMBER: 07027298 PATENT NUMBER: 4778815	FILING DATE: 03/18/1987 ISSUE DATE: 10/18/1988
SERIAL NUMBER: 06874772 PATENT NUMBER: 4798724	FILING DATE: 06/16/1986 ISSUE DATE: 01/17/1989
SERIAL NUMBER: 07042768 PATENT NUMBER: 4826832	FILING DATE: 04/27/1987 ISSUE DATE: 05/02/1989
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Assignee - Novartis Corp

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SERIAL NUMBER: 08185757 PATENT NUMBER: 5571788	FILING DATE: 01/24/1994 ISSUE DATE: 11/05/1996
SERIAL NUMBER: 08300668 PATENT NUMBER: 5583128	FILING DATE: 09/02/1994 ISSUE DATE: 12/10/1996
SERIAL NUMBER: 08288671 PATENT NUMBER: 5609868	FILING DATE: 08/10/1994 ISSUE DATE: 03/11/1997
SERIAL NUMBER: 08500988 PATENT NUMBER: 5633253	FILING DATE: 07/25/1995 ISSUE DATE: 05/27/1997
SERIAL NUMBER: 08207646 PATENT NUMBER: 5643878	FILING DATE: 03/08/1994 ISSUE DATE: 07/01/1997
SERIAL NUMBER: 08458926 PATENT NUMBER: 5648494	FILING DATE: 06/02/1995 ISSUE DATE: 07/15/1997
SERIAL NUMBER: 08426166 PATENT NUMBER: 5662928	FILING DATE: 04/21/1995 ISSUE DATE: 09/02/1997
SERIAL NUMBER: 08373910 PATENT NUMBER: 5663453	FILING DATE: 01/17/1995 ISSUE DATE: 09/02/1997
SERIAL NUMBER: 08750811 PATENT NUMBER: 5708024	FILING DATE: 12/17/1996 ISSUE DATE: 01/13/1998
SERIAL NUMBER: 08398416 PATENT NUMBER: 5728549	FILING DATE: 03/03/1995 ISSUE DATE: 03/17/1998
SERIAL NUMBER: 08731045 PATENT NUMBER: 5756338	FILING DATE: 10/08/1996 ISSUE DATE: 05/26/1998
SERIAL NUMBER: 08225488 PATENT NUMBER: 5846802	FILING DATE: 04/08/1994 ISSUE DATE: 12/08/1998
SERIAL NUMBER: 08459434 PATENT NUMBER: 5969116	FILING DATE: 06/02/1995 ISSUE DATE: 10/19/1999
SERIAL NUMBER: 08593312 PATENT NUMBER: 5695583	FILING DATE: 01/31/1996 ISSUE DATE: 12/09/1997
SERIAL NUMBER: 07595153 PATENT NUMBER: 5155130	FILING DATE: 10/10/1990 ISSUE DATE: 10/13/1992

SERIAL NUMBER: 07496183 FILING DATE: 03/20/1990
PATENT NUMBER: 5183749 ISSUE DATE: 02/02/1993

SERIAL NUMBER: 07763477 FILING DATE: 09/20/1991
PATENT NUMBER: 5204323 ISSUE DATE: 04/20/1993

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PATENT NUMBER: 5219346 ISSUE DATE: 06/15/1993

SERIAL NUMBER: 07867253 FILING DATE: 04/10/1992
PATENT NUMBER: 5229426 ISSUE DATE: 07/20/1993

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PATENT NUMBER: 5246699 ISSUE DATE: 09/21/1993

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PATENT NUMBER: 5268179 ISSUE DATE: 12/07/1993

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PATENT NUMBER: 5281747 ISSUE DATE: 01/25/1994

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PATENT NUMBER: 5290520 ISSUE DATE: 03/01/1994

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PATENT NUMBER: 5670491 ISSUE DATE: 09/23/1997

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PATENT NUMBER: 5708148 ISSUE DATE: 01/13/1998

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PATENT NUMBER: 5728676 ISSUE DATE: 03/17/1998

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PATENT NUMBER: 5977332 ISSUE DATE: 11/02/1999

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PATENT NUMBER: 5166212 ISSUE DATE: 11/24/1992

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PATENT NUMBER: 5189017 ISSUE DATE: 02/23/1993

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SERIAL NUMBER: 08041885 PATENT NUMBER: 5493009	FILING DATE: 04/02/1993 ISSUE DATE: 02/20/1996
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SERIAL NUMBER: 08331071 PATENT NUMBER: 5576439	FILING DATE: 10/28/1994 ISSUE DATE: 11/19/1996

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PATENT NUMBER: 5618690 ISSUE DATE: 04/08/1997

SERIAL NUMBER: 08427901 FILING DATE: 04/26/1995
PATENT NUMBER: 5637775 ISSUE DATE: 06/10/1997

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PATENT NUMBER: 5646143 ISSUE DATE: 07/08/1997

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PATENT NUMBER: 5700482 ISSUE DATE: 12/23/1997

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PATENT NUMBER: 5710124 ISSUE DATE: 01/20/1998

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PATENT NUMBER: 5807824 ISSUE DATE: 09/15/1998

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PATENT NUMBER: 5190930 ISSUE DATE: 03/02/1993

SERIAL NUMBER: 07915050 FILING DATE: 07/16/1992
PATENT NUMBER: 5211957 ISSUE DATE: 05/18/1993

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PATENT NUMBER: 5227393 ISSUE DATE: 07/13/1993

SERIAL NUMBER: 07849262 FILING DATE: 03/11/1992
PATENT NUMBER: 5238941 ISSUE DATE: 08/24/1993

SERIAL NUMBER: 07964184 FILING DATE: 10/21/1992
PATENT NUMBER: 5248693 ISSUE DATE: 09/28/1993

SERIAL NUMBER: 07988399 FILING DATE: 12/09/1992
PATENT NUMBER: 5270053 ISSUE DATE: 12/14/1993

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PATENT NUMBER: 5296475 ISSUE DATE: 03/22/1994

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PATENT NUMBER: 5321027 ISSUE DATE: 06/14/1994

SERIAL NUMBER: 08048395 FILING DATE: 04/14/1993
PATENT NUMBER: 5344825 ISSUE DATE: 09/06/1994

SERIAL NUMBER: 08113551 FILING DATE: 08/27/1993
PATENT NUMBER: 5371096 ISSUE DATE: 12/06/1994

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PATENT NUMBER: 5393885 ISSUE DATE: 02/28/1995

SERIAL NUMBER: 08266153 FILING DATE: 06/27/1994
PATENT NUMBER: 5416102 ISSUE DATE: 05/16/1995

SERIAL NUMBER: 07632584 FILING DATE: 12/21/1990
PATENT NUMBER: 5428160 ISSUE DATE: 06/27/1995

SERIAL NUMBER: 08306864 FILING DATE: 09/15/1994
PATENT NUMBER: 5457209 ISSUE DATE: 10/10/1995

SERIAL NUMBER: 08258902 FILING DATE: 06/13/1994
PATENT NUMBER: 5466585 ISSUE DATE: 11/14/1995

SERIAL NUMBER: 08328961 FILING DATE: 10/24/1994
PATENT NUMBER: 5501975 ISSUE DATE: 03/26/1996

SERIAL NUMBER: 08238115 FILING DATE: 05/04/1994
PATENT NUMBER: 5532287 ISSUE DATE: 07/02/1996

SERIAL NUMBER: 08461090 FILING DATE: 06/05/1995
PATENT NUMBER: 5567840 ISSUE DATE: 10/22/1996

SERIAL NUMBER: 08311848 FILING DATE: 09/23/1994
PATENT NUMBER: 5580559 ISSUE DATE: 12/03/1996

SERIAL NUMBER: 07797500 FILING DATE: 11/22/1991
PATENT NUMBER: 5599503 ISSUE DATE: 02/04/1997

SERIAL NUMBER: 08687878 FILING DATE: 07/25/1996
PATENT NUMBER: 5627182 ISSUE DATE: 05/06/1997

SERIAL NUMBER: 08436368 FILING DATE: 07/25/1995
PATENT NUMBER: 5639768 ISSUE DATE: 06/17/1997

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
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Washington, D.C. 20231

SERIAL NUMBER: 08482704 PATENT NUMBER: 5646144	FILING DATE: 06/07/1995 ISSUE DATE: 07/08/1997
SERIAL NUMBER: 08680731 PATENT NUMBER: 5654468	FILING DATE: 07/15/1996 ISSUE DATE: 08/05/1997
SERIAL NUMBER: 08544525 PATENT NUMBER: 5663336	FILING DATE: 10/18/1995 ISSUE DATE: 09/02/1997
SERIAL NUMBER: 08573102 PATENT NUMBER: 5686439	FILING DATE: 12/15/1995 ISSUE DATE: 11/11/1997
SERIAL NUMBER: 08556979 PATENT NUMBER: 5702724	FILING DATE: 12/06/1995 ISSUE DATE: 12/30/1997
SERIAL NUMBER: 08444848 PATENT NUMBER: 5712249	FILING DATE: 05/19/1995 ISSUE DATE: 01/27/1998
SERIAL NUMBER: 08444344 PATENT NUMBER: 5739290	FILING DATE: 05/18/1995 ISSUE DATE: 04/14/1998
SERIAL NUMBER: 08592419 PATENT NUMBER: 5827984	FILING DATE: 02/06/1996 ISSUE DATE: 10/27/1998
SERIAL NUMBER: 07725222 PATENT NUMBER: 5925372	FILING DATE: 06/26/1991 ISSUE DATE: 07/20/1999

SHARON LATIMER, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

4,459,298	4,470,988	4,473,575	4,476,132	4,477,464
4,478,842	4,492,691	4,510,128	4,511,567	4,511,573
4,512,987	4,524,146	4,540,514	4,548,923	4,551,475
4,559,174	4,559,332	4,559,349	4,560,770	4,563,457
4,579,683	4,579,684	4,582,852	4,584,314	4,588,732
4,590,292	4,591,642	4,595,684	4,599,357	4,600,719
4,602,014	4,604,397	4,617,307	4,619,921	4,619,926
4,649,149	4,654,302	4,666,441	4,668,781	4,677,127
4,678,800	4,680,172	4,687,855	4,690,927	4,692,442
4,692,469	4,696,922	4,696,945	4,697,020	4,707,476
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4,749,713	4,764,640	4,765,985	4,778,809	4,778,814
4,778,815	4,782,014	4,783,468	4,784,808	4,791,134
4,798,724	4,798,837	4,801,576	4,804,661	4,824,868
4,826,832	4,831,013	4,837,255	4,839,379	4,853,227
4,855,317	4,857,336	4,857,509	4,857,660	4,859,657
4,859,736	4,871,719	4,871,720	4,873,086	4,885,166
4,889,861	4,892,739	4,897,416	4,897,486	4,911,707
4,913,905	4,917,676	4,917,886	4,918,097	4,920,148
4,925,875	4,927,507	4,937,250	4,939,130	4,952,690
4,954,346	4,959,386	4,962,105	4,965,074	4,968,615
4,968,697	4,971,670	4,971,802	4,971,981	4,971,986
4,973,589	4,973,711	4,977,144	4,978,677	4,980,506
4,988,675	4,989,974	4,994,440	4,996,058	4,998,797
5,002,940	5,004,781	5,013,863	5,026,841	5,034,381
5,051,524	5,054,867	5,064,654	5,064,761	5,064,819
5,066,793	5,068,515	5,071,761	5,071,861	5,073,539
5,079,001	5,082,548	5,091,184	5,091,520	5,093,330
5,093,530	5,096,717	5,096,925	5,098,841	5,098,911
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5,175,348	5,180,718	5,183,749	5,189,017	5,190,930
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5,229,379	5,229,405	5,229,426	5,236,706	5,238,941
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5,272,059	5,274,188	5,281,747	5,283,067	5,286,728
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5,322,852	5,332,729	5,334,583	5,342,977	5,344,825
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5,726,043	5,728,549	5,728,676	5,728,708	5,739,290
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5,837,734	5,846,802	5,866,124	5,922,569	5,925,372
5,939,531	5,969,116	5,977,332		

State of New York
Department of State

ss:

I hereby certify, that the certificate of incorporation of NOVARTIS CORPORATION was filed on 11/15/1966, under the name of ARDSLEY CHEMICAL CORPORATION, with perpetual duration, and that a diligent examination has been made of the index of corporation papers filed in this Department for a certificate, order, or record of a dissolution, and upon such examination, no such certificate, order or record has been found, and that so far as indicated by the records of this Department, such corporation is a subsisting corporation. I further certify the following:

A Certificate of Merger and Name Change of ARDSLEY CHEMICAL CORPORATION, changing name to GEIGY CHEMICAL CORPORATION was filed on 12/30/1966.

A Certificate of Merger and Name Change of GEIGY CHEMICAL CORPORATION, changing name to CIBA-GEIGY CORPORATION was filed on 10/21/1970.

A Certificate of Amendment was filed on 12/19/1972.

A Certificate of Merger was filed on 12/29/1972.

A Certificate of Merger was filed on 12/19/1974.

A Certificate of Merger was filed on 12/24/1974.

A Certificate of Merger was filed on 12/26/1974.

A Certificate of Amendment was filed on 01/22/1979.

A Certificate of Amendment was filed on 08/24/1979.

A Certificate of Merger was filed on 12/26/1979.

A Certificate of Merger was filed on 12/26/1979.

A Certificate of Merger was filed on 11/02/1981.

A Certificate of Merger was filed on 12/17/1981.

A Certificate of Merger was filed on 12/29/1983.

A Certificate of Merger was filed on 12/19/1984.

A Certificate of Merger was filed on 03/31/1987.

A Certificate of Merger was filed on 06/26/1987.

A Certificate of Merger was filed on 01/26/1988.

A Certificate of Merger was filed on 12/30/1988.

A Certificate of Merger was filed on 12/23/1991.

A Certificate of Merger was filed on 12/23/1991.

A Certificate of Merger was filed on 12/23/1991.

A Certificate of Merger was filed on 05/22/1992.

A Biennial Statement was filed 12/10/1992.

A Certificate of Merger was filed on 12/22/1992.

A Biennial Statement was filed 12/09/1993.

Certificate of change was filed on 06/02/1995.

A Certificate of Merger and Name Change of CIBA-GEIGY CORPORATION, changing name to NOVARTIS CORPORATION was filed on 12/31/1996.

Certificate of change was filed on 04/14/1997.

The Corporation Biennial Statement is past due.

I further certify, that no other certificates have been filed by such corporation.

Witness my hand and the official seal of the Department of State at the City of Albany, this 12th day of June one thousand nine hundred and ninety-seven.

Special Deputy Secretary of State

199706130195 37

FORM PTO-1595 (Rev. 6-93)
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10-11-2000

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U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):
Ciba-Geigy Corporation

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies)
Name: Novartis Corporation
Internal Address:
Street Address: 608 Fifth Avenue
City: New York State: NY ZIP: 10020
Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:
☐ Assignment ☐ Merger
☐ Security Agreement ☒ Change of Name
☐ Other
Execution Date:

4. Application number(s) or patent number(s): MRD 8.22.00
If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s)

B. Patent No.(s)
D352,107 4,409,212 4,424,221 4,444,775

Additional numbers attached? ☒ Yes ☐ No

5. Name and address of party to whom correspondence concerning document should be mailed:
Name: Thomas Hoxie
Internal Address: Novartis Corporation
Patent and Trademark Dept.
Street Address: 564 Morris Avenue
City: Summit State: NJ ZIP: 07901-1027

6. Total number of applications and patents involved: 337

7. Total fee (37 CFR 3.41) $ 13,480
☐ Enclosed
☒ Authorized to be charged to deposit account and any other additional fees required.

8. Deposit account number:
19-0134 (in the name of Novartis Corporation)
(Attach duplicate copy of this page if paying by deposit account)

10/10/2000 MTHAI1 00000041 190134 D352107
01 FC:581 13480.00 CH

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9. Statement and signature.
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Melvyn M. Kassenoff — Name of Person Signing
Reg. No. 26,389

Melvyn M. Kassenoff — Signature

August 18, 2000 — Date

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State of New York
Department of State | ss:

I hereby certify, that the certificate of incorporation of NOVARTIS CORPORATION was filed on 11/15/1966, under the name of ARDSLEY CHEMICAL CORPORATION, with perpetual duration, and that a diligent examination has been made of the index of corporation papers filed in this Department for a certificate, order, or record of a dissolution, and upon such examination, no such certificate, order or record has been found, and that so far as indicated by the records of this Department, such corporation is a subsisting corporation. I further certify the following:

A Certificate of Merger and Name Change of ARDSLEY CHEMICAL CORPORATION, changing name to GEIGY CHEMICAL CORPORATION was filed on 12/30/1966.

A Certificate of Merger and Name Change of GEIGY CHEMICAL CORPORATION, changing name to CIBA-GEIGY CORPORATION was filed on 10/21/1970.

A Certificate of Amendment was filed on 12/19/1972.

A Certificate of Merger was filed on 12/29/1972.

A Certificate of Merger was filed on 12/19/1974.

A Certificate of Merger was filed on 12/24/1974.

A Certificate of Merger was filed on 12/26/1974.

A Certificate of Amendment was filed on 01/22/1979.

A Certificate of Amendment was filed on 08/24/1979.

A Certificate of Merger was filed on 12/26/1979.

A Certificate of Merger was filed on 12/26/1979.

A Certificate of Merger was filed on 11/02/1981.

A Certificate of Merger was filed on 12/17/1981.

A Certificate of Merger was filed on 12/29/1983.

A Certificate of Merger was filed on 12/19/1984.

A Certificate of Merger was filed on 03/31/1987.

A Certificate of Merger was filed on 06/26/1987.

A Certificate of Merger was filed on 01/26/1988.

A Certificate of Merger was filed on 12/30/1988.

A Certificate of Merger was filed on 12/23/1991.

A Certificate of Merger was filed on 12/23/1991.

A Certificate of Merger was filed on 12/23/1991.

A Certificate of Merger was filed on 05/22/1992.

A Biennial Statement was filed 12/10/1992.

A Certificate of Merger was filed on 12/22/1992.

A Biennial Statement was filed 12/09/1993.

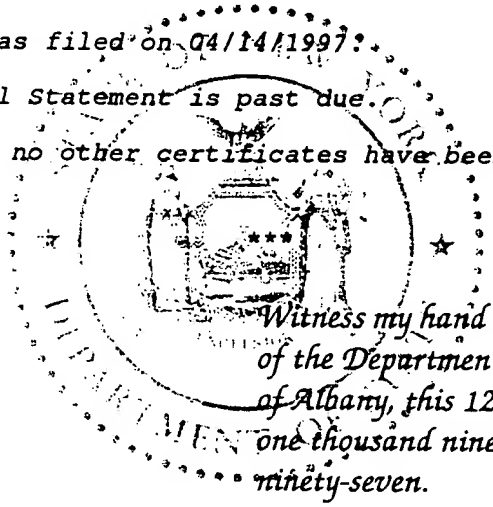
Certificate of change was filed on 06/02/1995.

A Certificate of Merger and Name Change of CIBA-GEIGY CORPORATION, changing name to NOVARTIS CORPORATION was filed on 12/31/1996.

Certificate of change was filed on 04/14/1997.

The Corporation Biennial Statement is past due.

I further certify, that no other certificates have been filed by such corporation.



Witness my hand and the official seal of the Department of State at the City of Albany, this 12th day of June one thousand nine hundred and ninety-seven.

Special Deputy Secretary of State

199706130195 37

APPENDIX B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE U.S. PATENT NO. 5,559,111

ISSUED: September 24, 1996

INVENTORS: RICHARD GÖSCHKE, JÜRGEN K. MAIBAUM, WALTER SCHILLING, STEFAN STUTZ, PASCAL RIGOLLIER, YASUCHIKA YAMAGUCHI, NISSIM CLAUDE COHEN AND PETER HEROLD

FOR: δ-AMINO-γ-HYDROXY-ω-ARYL-ALKANOIC-ACID AMIDES

Assistant Commissioner for Patents
Washington, D.C. 20231

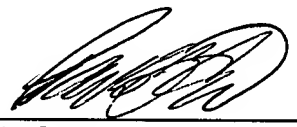
POWER OF ATTORNEY

Sir:

Novartis Corporation, a New York Corporation having offices at 608 Fifth Avenue, New York, New York 10020, being the owner of the entire right, title and interest in and to U.S. Patent No. 5,559,111, which was granted on September 24, 1996 to Richard Göschke, Jürgen K. Maibaum, Walter Schilling, Stefan Stutz, Pascal Rigollier, Yasuchika Yamaguchi, Nissim C. Cohen and Peter Herold and entitled "δ-AMINO-γ-HYDROXY-ω-ARYL-ALKANOIC-ACID AMIDES", hereby appoints the attorneys and agents associated with customer No. 001095, respectively and individually, each of them with full power of substitution and revocation, to prosecute this application and to transact all business in the U.S. Patent and Trademark Office connected herewith.

Please direct all telephone calls to Gregory D. Ferraro at (862) 778-7831, and all correspondence to Novartis, Corporate Intellectual Property, One Health Plaza, Bldg. 104, East Hanover, New Jersey 07936-1080.

NOVARTIS CORPORATION



Paulo Costa
President & CEO, Novartis Corporation

Date:

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-985

APPENDIX C

Novartis Pharmaceuticals Corporation
Attention: Kimberly D. Dickerson, Pharm.D.
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Dickerson:

Please refer to your new drug application (NDA) dated February 10, 2006, received February 13, 2006, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Tekturna (aliskiren) 150 mg and 300 mg Tablets.

We acknowledge receipt of your submissions dated March 13, 14, 17, 31, April 3, 4, 5, 19 (twice), May 2, June 13, 22, 27, 28, July 5, 6, August 1, 14, 16, 31, September 15, 26, 28, October 4, 5, 6, 13, 17, 25, 26, November 2, 3 (twice), 9, 15, 16, 17, 21, 29, 30, December 1, 4, 8, 14, 20, 2006, and January 12, 26, February 26 (twice), 27 (twice), 28 and March 5, 2007.

This new drug application provides for the use of Tekturna (aliskiren) 150 mg and 300 mg Tablets for the treatment of hypertension.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and text for the patient package insert) and submitted labeling (immediate container and carton labels submitted January 26, 2007). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless the requirement is waived or deferred. We reference the deferral granted on August 26, 2004, for the pediatric study requirement for this application. We have reviewed your submission and agree that a partial waiver is justified for pediatric studies in patients 0-6 years due to too few patients < 6 years to study. We are deferring submission of your pediatric studies for ages 6 to 16 years until March 5, 2007.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for the treatment of hypertension in pediatric patients ages 6 to 16 years.
   Final Report Submission: March 5, 2009

Submit final study reports to this NDA. For administrative purposes, all submissions related to pediatric postmarketing study commitment must be clearly designated "**Required Pediatric Study Commitments**".

We remind you of your other postmarketing study commitments in your submission dated February 27 and March 5, 2007. These commitments are listed below.

2. To establish an assay method and acceptance criterion for Synthon B (SPP100 B2). Assay method and assay specification will be introduced into the testing monograph No. RM_5000702 for Synthon B post approval by March 2007. The revised testing monograph will be submitted to FDA in the first NDA Annual Report.
3. To re-evaluate the specifications for the water content when further data are available from the additional manufacturing sites. You expect to have this data evaluation completed by June 2007.
   Final Report Submission: by 08/07
4. To submit the results of the cellular markers of proliferation and apoptosis from Study 2103 as soon as they are available, but no later than September 2007.
   Final Report Submission: by 09/07
5. To include intestinal procedures and neoplasms and angioedema as events of special interest in your proposed ALTITUDE trial as detailed in their special protocol assessment letters. You committed to providing safety information and periodic summaries during the ALTITUDE trial for the parameters of special interest. The data should be submitted when the final study report comes in. The periodic summaries will include:
   - Monthly line listings of suspected/non suspected SAE and non serious AE (reported in the previous month)
   - Aggregate summaries (cumulative) of suspected/non suspected SAE and non serious AE in PSUR semi-annually for the first 2 years post-launch and annually thereafter.

   Protocol Submission (including case report forms): by 09/07
   Study Completion Date: by 09/11
   Final Report Submission: by 03/12
6. To incorporate a colonoscopy substudy into your proposed long-term outcome study. The colonoscopy substudy should include colonoscopies performed at baseline and after drug treatment for 12 months or longer. This study should be powered to rule out a doubling in the rate of cancerous or precancerous lesions. You should discuss this substudy with the Agency.
   Protocol Submission: by 09/07
   Study Completion Date: by 02/09
   Final Report Submission: by 05/09
7. You should provide evidence that it is not likely to be clinically useful to give aliskiren in a twice-daily dosing regimen to patients whose blood pressure is not controlled on the highest recommended dose given once daily. These data could come from a study comparing once- and twice-daily dosing, but the Division would consider alternative strategies to address this issue.
   Protocol Agreement: by 06/07
   Final Report Submission: by 02/09

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence.**"

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division

of Cardiovascular and Renal Products and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

An expiry of 24 months for Tekturna (aliskiren) 150 mg and 300 mg is granted.

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, please call Mr. John David, Regulatory Health Project Manager, at (301) 796-1059.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: enclosed labeling (text for the package insert and text for the patient package insert)

Tekturna®
(aliskiren)
Tablets
150 mg and 300 mg

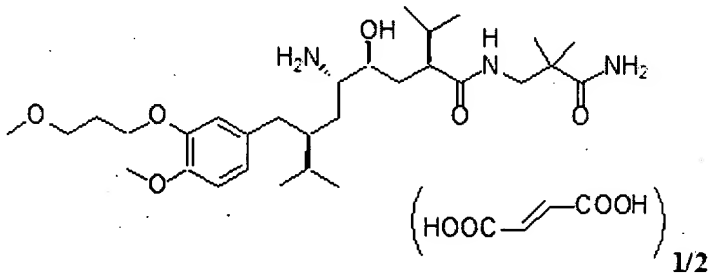
Rx only

Prescribing Information

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Tekturna should be discontinued as soon as possible. See **WARNINGS: Fetal/Neonatal Morbidity and Mortality.**

DESCRIPTION

Aliskiren, the active component of Tekturna® Tablets, is an orally active, nonpeptide, potent renin inhibitor. Aliskiren is present in Tekturna Tablets as its hemifumarate salt. Aliskiren hemifumarate is chemically described as (2S,4S,5S,7S)-N-(2-Carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]-octanamide hemifumarate and its structural formula is



Molecular formula: $C_{30}H_{53}N_3O_6 \cdot 0.5\ C_4H_4O_4$

Aliskiren hemifumarate is a white to slightly yellowish crystalline powder with a molecular weight of 609.8 (free base- 551.8). It is soluble in phosphate buffer, n-Octanol, and highly soluble in water. Tekturna is available for oral administration as film-coated tablets containing 150 mg, and 300 mg of aliskiren base and the following inactive ingredients: colloidal silicon dioxide, crospovidone, hypromellose, iron oxide colorants, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action
Renin is secreted by the kidney in response to decreases in blood volume and renal perfusion. Renin cleaves angiotensinogen to form the inactive decapeptide angiotensin I (Ang I). Ang I is converted to

the active octapeptide angiotensin II (Ang II) by angiotensin-converting enzyme (ACE) and non-ACE pathways. Ang II is a powerful vasoconstrictor and leads to the release of catecholamines from the adrenal medulla and prejunctional nerve endings. It also promotes aldosterone secretion and sodium reabsorption. Together, these effects increase blood pressure. Ang II also inhibits renin release, thus providing a negative feedback to the system. This cycle, from renin through angiotensin to aldosterone and its associated negative feedback loop, is known as the renin-angiotensin-aldosterone system (RAAS). Aliskiren is a direct renin inhibitor, decreasing plasma renin activity (PRA) and inhibiting the conversion of angiotensinogen to Ang I. Whether aliskiren affects other RAAS components, e.g., ACE or non-ACE pathways, is not known.

All agents that inhibit the RAAS, including renin inhibitors, suppress the negative feedback loop, leading to a compensatory rise in plasma renin concentration. When this rise occurs during treatment with ACE inhibitors and ARBs, the result is increased levels of PRA. During treatment with aliskiren, however, the effect of increased renin levels is blocked, so that PRA, Ang I and Ang II are all reduced, whether aliskiren is used as monotherapy or in combination with other antihypertensive agents. PRA reductions in clinical trials ranged from approximately 50%-80%, were not dose-related and did not correlate with blood pressure reductions. The clinical implications of the differences in effect on PRA are not known.

Pharmacokinetics
Aliskiren is a poorly absorbed (bioavailability about 2.5%) drug with an approximate accumulation half life of 24 hours. Steady-state blood levels are reached in about 7-8 days.

Absorption and Distribution
Following oral administration, peak plasma concentrations of aliskiren are reached within 1 to 3 hours. When taken with a high fat meal, mean AUC and C_{max} of aliskiren are decreased by 71% and 85%, respectively. In the clinical trials of aliskiren, it was administered without requiring a fixed relation of administration to meals.

Metabolism and Elimination
About one-fourth of the absorbed dose appears in the urine as parent drug. How much of the absorbed dose is metabolized is unknown. Based on the in vitro studies, the major enzyme responsible for aliskiren metabolism appears to be CYP 3A4.

Special Populations

Pediatric
The pharmacokinetics of aliskiren have not been investigated in patients <18 years of age.

Geriatric
The pharmacokinetics of aliskiren were studied in the elderly (≥65 years). Exposure (measured by AUC) is increased in elderly patients. Adjustment of the starting dose is not required in these patients (see DOSAGE AND ADMINISTRATION).

Race
The pharmacokinetic differences between Blacks, Caucasians and the Japanese are minimal.

Renal Insufficiency
The pharmacokinetics of aliskiren were evaluated in patients with varying degrees of renal insufficiency. Rate and extent of exposure (AUC and C_{max}) of aliskiren in subjects with renal impairment did not show a consistent correlation with the severity of renal impairment. Adjustment of the starting dose is not required in these patients (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency
The pharmacokinetics of aliskiren were not significantly affected in patients with mild-to- severe liver disease. Consequently, adjustment of the starting dose is not required in these patients (see DOSAGE AND ADMINISTRATION).

Cardiac Electrophysiology
Aliskiren's effects on ECG intervals were studied in a randomized, double-blind, placebo and active-controlled (moxifloxacin), 7-day repeat dosing study with Holter-monitoring and 12-lead ECGs throughout the interdosing interval. No effect of aliskiren on QT interval was seen.

Drug Interactions

Effects of Other Drugs on Aliskiren
Based on in-vitro studies, aliskiren is metabolized by CYP 3A4.
Co-administration of lovastatin, atenolol, warfarin, furosemide, digoxin, celecoxib, hydrochlorothiazide, ramapril, valsartan, metformin and amlodipine did not result in clinically significant increases in aliskiren exposure.
Co-administration of irbesartan reduced aliskiren C_{max} up to 50% after multiple dosing.
Co-administration of atorvastatin resulted in about a 50% increase in aliskiren C_{max} and AUC after multiple dosing.

Ketoconazole
Co-administration of 200 mg twice-daily ketoconazole with aliskiren resulted in an approximate 80% increase in plasma levels of aliskiren. A 400 mg once-daily dose was not studied but would be expected to increase aliskiren blood levels further.

Effects of Aliskiren on Other Drugs
Aliskiren does not inhibit the CYP450 isoenzymes (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1, and CYP 3A) or induce CYP 3A4.
Co-administration of aliskiren did not significantly affect the pharmacokinetics of lovastatin, digoxin, valsartan, amlodipine, metformin, celecoxib, atenolol, atorvastatin, ramipril or hydrochlorothiazide.

Warfarin
The effects of aliskiren on warfarin pharmacokinetics have not been evaluated in a well-controlled clinical trial.

Furosemide
When aliskiren was co-administered with furosemide, the AUC and C_{max} of furosemide were reduced by about 30% and 50%, respectively.

CLINICAL TRIALS

Aliskiren Monotherapy

The antihypertensive effects of Tekturna® (aliskiren) have been demonstrated in six randomized, double-blind, placebo-controlled 8-week clinical trials in patients with mild-to-moderate hypertension. The placebo response and placebo-subtracted changes from baseline in seated trough cuff blood pressure are shown in Table 1.

Table 1: Reductions in Seated Trough Cuff Blood Pressure in the Placebo-Controlled Studies

		Aliskiren daily dose, mg			
Study	Placebo	75	150	300	600
	Mean change	Placebo-subtracted	Placebo-subtracted	Placebo-subtracted	Placebo-subtracted
1	2.9/3.3	5.7/4*	5.9/4.5*	11.2/7.5*	--
2	5.3/6.3	--	6.1/2.9*	10.5/5.4*	10.4/5.2*
3	10/8.6	2.2/1.7	2.1/1.7	5.1/3.7*	--
4	7.5/6.9	1.9/1.8	4.8/2*	8.3/3.3*	--
5	3.8/4.9	--	9.3/5.4*	10.9/6.2*	12.1/7.6*
6	4.6/4.1	--	--	8.4/4.9†	--

*p<0.05 vs. placebo by ANCOVA with Dunnett's procedure for multiple comparisons
†p<0.05 vs. placebo by ANCOVA for the pairwise comparison.

The studies included approximately 2730 patients given doses of 75-600 mg of aliskiren and 1231 patients given placebo. As shown in Table 1, there is some increase in response with administered dose in all studies, with reasonable effects seen at 150-300 mg, and no clear further increase at 600 mg. A substantial proportion (85%-90%) of the blood pressure lowering effect was observed within 2 weeks of treatment. Studies with ambulatory blood pressure monitoring showed reasonable control throughout the interdosing interval; the ratios of mean daytime to mean nighttime ambulatory BP ranged from 0.6 to 0.9.

Patients in the placebo-controlled trials continued open-label aliskiren for up to one year. A persistent blood pressure lowering effect was demonstrated by a randomized withdrawal study (patients randomized to continued drug or placebo), which showed a statistically significant difference between patients kept on aliskiren and those randomized to placebo. With cessation of treatment, blood pressure gradually returned toward baseline levels over a period of several weeks. There was no evidence of rebound hypertension after abrupt cessation of therapy.

Aliskiren lowered blood pressure in all demographic subgroups, although Black patients tended to have smaller reductions than Caucasians and Asians, as has been seen with ACE inhibitors and ARBs.

Aliskiren in Combination with Other Antihypertensives

Aliskiren 75, 150, and 300 mg and hydrochlorothiazide 6.25, 12.5, and 25 mg were studied alone and in combination in an 8-week, 2,776-patient, randomized, double-blind, placebo-controlled, parallel-group, 15-arm factorial study. Blood pressure reductions with the combinations were greater than the reductions with the monotherapies as shown in Table 2.

Diuretics

Table 2: Placebo-Subtracted Reductions in Seated Trough Cuff Blood Pressure in Combination with Hydrochlorothiazide

		Hydrochlorothiazide, mg			
Aliskiren, mg	Placebo mean change	0	6.25	12.5	25
		Placebo-subtracted	Placebo-subtracted	Placebo-subtracted	Placebo-subtracted
0	7.5/6.9	--	3.5/2.1	6.4/3.2	6.8/2.4
75	--	1.9/1.8	6.8/3.8	8.2/4.2	9.8/4.5
150	--	4.8/2	7.8/3.4	10.1/5	12/5.7
300	--	8.3/3.3	--	12.3/7	13.7/7.3

Valsartan

Aliskiren 150 and 300 mg and valsartan 160 and 320 mg were studied alone and in combination in an 8-week, 1,797-patient, randomized, double-blind, placebo-controlled, parallel-group, 4-arm, dose-escalation study. The dosages of aliskiren and valsartan were started at 150 and 160 mg, respectively, and increased at four weeks to 300 mg and 320 mg, respectively. Seated trough cuff blood pressure was measured at baseline, 4, and 8 weeks. Blood pressure reductions with the combinations were greater than the reductions with the monotherapies as shown in Table 3.

Table 3: Placebo-Subtracted Reductions in Seated Trough Cuff Blood Pressure in Combination with Valsartan

Aliskiren mg	Placebo mean change	Valsartan, mg		
		0	160	320
0	4.6/4.1*	--	5.6/3.9	8.2/5.6
150	--	5.4/2.7	10.0/5.7	--
300	--	8.4/4.9	--	12.6/8.1

* The placebo change is 5.2/4.8 for week 4 endpoint which was used for the dose groups containing Aliskiren 150 mg or Valsartan 160 mg.

ACE inhibitors and Amlodipine

Aliskiren has not been studied when added to maximal doses of ACE inhibitors to determine whether aliskiren produces additional blood pressure reduction with a maximal dose of an ACE inhibitor. Aliskiren 150 mg provided additional blood pressure reduction when co-administered with amlodipine 5 mg in one study, but the combination was not statistically significantly better than amlodipine 10 mg.

INDICATIONS AND USAGE

Tekturna® (aliskiren) is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents. Use with maximal doses of ACE inhibitors has not been adequately studied.

WARNINGS

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. When pregnancy is detected, Tekturna® (aliskiren) should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug. These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to a renin inhibitor only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should advise the patient to discontinue the use of Tekturna as soon as possible. Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, Tekturna should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Infants with histories of in-utero exposure to a renin inhibitor should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

There is no clinical experience with the use of Tekturna in pregnant women. Reproductive toxicity studies of aliskiren hemifumarate did not reveal any evidence of teratogenicity at oral doses up to 600 mg aliskiren/kg/day (20 times the maximum recommended human dose (MRHD) of 300 mg/day on a mg/m^2 basis) in pregnant rats or up to 100 mg aliskiren/kg/day (seven times the MRHD on a mg/m^2 basis) in pregnant rabbits. Fetal birth weight was adversely affected in rabbits at 50 mg/kg/day (3.2 times the MRHD on a mg/m^2 basis). Aliskiren was present in placenta, amniotic fluid and fetuses of pregnant rabbits.

Head and Neck Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with aliskiren. This may occur at any time during treatment. ACE inhibitors have been associated with a higher rate of angioedema in Black than in non-Black patients, but whether angioedema rates are higher in Blacks with aliskiren is not known. Tekturna should be promptly discontinued and appropriate therapy and monitoring provided until complete and sustained resolution of signs and symptoms has occurred. Experience with ACE inhibitors indicates that even in those instances where only swelling of the tongue is seen initially, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient to prevent respiratory involvement. Very rarely, fatalities have been reported in patients with angioedema associated with laryngeal edema or tongue edema with ACE inhibitors. Patients with involvement of the tongue, glottis or larynx are more likely to experience airway obstruction, especially those with a history of airway surgery. Where there is involvement of the tongue, glottis or larynx, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and

measures necessary to ensure a patent airway should be promptly provided (see ADVERSE REACTIONS).

Hypotension
An excessive fall in blood pressure was rarely seen (0.1%) in patients with uncomplicated hypertension treated with Tekturna alone. Hypotension was also infrequent during combination therapy with other antihypertensive agents (<1%). In patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients (e.g., those receiving high doses of diuretics), symptomatic hypotension could occur after initiation of treatment with Tekturna. This condition should be corrected prior to administration of Tekturna, or the treatment should start under close medical supervision.

If an excessive fall in blood pressure occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline (see DOSAGE AND ADMINISTRATION). A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

PRECAUTIONS

General

Impaired Renal Function
Patients with greater than moderate renal dysfunction (creatinine 1.7 mg/dL for women and 2.0 mg/dL for men and/or estimated GFR <30mL/min), a history of dialysis, nephrotic syndrome, or renovascular hypertension were excluded from clinical trials of Tekturna® (aliskiren) in hypertension. Caution should be exercised in these patients because of the paucity of safety information with Tekturna in these patients and the potential for other drugs acting on the renin-angiotensin system to increase serum creatinine and blood urea nitrogen.

Hyperkalemia
Increases in serum potassium > 5.5 meq/L were infrequent with Tekturna alone (0.9% compared to 0.6% with placebo). However, when used in combination with an ACE inhibitor in a diabetic population, increases in serum potassium were more frequent (5.5%). Routine monitoring of electrolytes and renal function is indicated in this population.

Information for Patients

Pregnancy
Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Angioedema
Angioedema, including laryngeal edema, may occur at any time during treatment with Tekturna. Patients should be so advised and told to report immediately any signs or symptoms suggesting

angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Drug Interactions
Patients should report any medications they take with aliskiren.

Furosemide
When aliskiren was given with furosemide, the blood concentrations of furosemide were reduced significantly. Patients receiving furosemide could find its effect diminished after starting aliskiren.

Carcinogenesis/Mutagenesis/Impairment of Fertility
Carcinogenic potential was assessed in a 2-year rat study and a 6-month transgenic (rasH2) mouse study with aliskiren hemifumarate at oral doses of up to 1500 mg aliskiren/kg/day. Although there were no statistically significant increases in tumor incidence associated with exposure to aliskiren, mucosal epithelial hyperplasia (with or without erosion/ulceration) was observed in the lower gastrointestinal tract at doses of 750 or more mg/kg/day in both species, with a colonic adenoma identified in one rat and a cecal adenocarcinoma identified in another, rare tumors in the strain of rat studied. On a systemic exposure ($AUC_{0\text{-}24hr}$) basis, 1500 mg/kg/day in the rat is about 4 times, and is in the mouse about 1.5 times, the maximum recommended human dose (300 mg aliskiren/day). Mucosal hyperplasia in the cecum or colon of rats was also observed at oral doses of 250 mg/kg/day (the lowest tested dose) as well as at higher doses in 4- and 13-week studies.

Aliskiren hemifumarate was devoid of genotoxic potential in the Ames reverse mutation assay with *S. typhimurium* and *E. coli*, the in vitro Chinese hamster ovary cell chromosomal aberration assay, the in vitro Chinese hamster V79 cell gene mutation test and the in vivo mouse bone marrow micronucleus assay.

Fertility of male and female rats was unaffected at doses of up to 250 mg aliskiren/kg/day (8 times the maximum recommended human dose of 300 mg Tekturna/60 kg on a mg/m^2 basis.

Pregnancy
Pregnancy Categories C (first trimester) and D (second and third trimesters) (see WARNINGS, Fetal/Neonatal Morbidity and Mortality).

Nursing Mothers
It is not known whether aliskiren is excreted in human milk. Aliskiren was secreted in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness of aliskiren in pediatric patients have not been established.

Geriatric Use
Of the total number of patients receiving aliskiren in clinical studies, 1,275 (19 %) were 65 years or older and 231 (3.4%) were 75 years or older. Blood pressure responses and adverse effects were generally similar to those in younger patients

ADVERSE REACTIONS

Tekturna® (aliskiren) has been evaluated for safety in more than 6,460 patients, including over 1,740 treated for longer than 6 months, and more than 1,250 for longer than 1 year. In placebo-controlled clinical trials, discontinuation of therapy due to a clinical adverse event, including uncontrolled hypertension occurred in 2.2% of patients treated with Tekturna, vs 3.5% of patients given placebo.

Two cases of angioedema with respiratory symptoms were reported with aliskiren use in the clinical studies. Two other cases of periorbital edema without respiratory symptoms were reported as possible angioedema and resulted in discontinuation. The rate of these angioedema cases in the completed studies was 0.06 %.

In addition, 26 other cases of edema involving the face, hands, or whole body were reported with aliskiren use, including 4 leading to discontinuation. In the placebo controlled studies, however, the incidence of edema involving the face, hands or whole body was 0.4% with aliskiren compared with 0.5% with placebo. In a long term active control study with aliskiren and HCTZ arms, the incidence of edema involving the face, hand or whole body was 0.4% in both treatment arms.

Aliskiren produces dose-related gastrointestinal (GI) adverse effects. Diarrhea was reported by 2.3% of patients at 300 mg, compared to 1.2% in placebo patients. In women and the elderly (age $\geq$ 65) increases in diarrhea rates were evident starting at a dose of 150 mg daily, with rates for these subgroups at 150 mg comparable to those seen at 300 mg for men or younger patients (all rates about 2.0%-2.3%). Other GI symptoms included abdominal pain, dyspepsia, and gastroesophageal reflux, although increased rates for abdominal pain and dyspepsia were distinguished from placebo only at 600 mg daily. Diarrhea and other GI symptoms were typically mild and rarely led to discontinuation. Aliskiren was associated with a slight increase in cough in the placebo-controlled studies (1.1% for any aliskiren use vs. 0.6% for placebo). In active-controlled trials with ACE inhibitor (ramipril, lisinopril) arms, the rates of cough for the aliskiren arms were about one-third to one-half the rates in the ACE inhibitor arms.

Other adverse effects with increased rates for aliskiren compared to placebo included rash (1% vs. 0.3%), elevated uric acid (0.4% vs. 0.1%), gout (0.2% vs. 0.1%), and renal stones (0.2% vs. 0%). Single episodes of tonic-clonic seizures with loss of consciousness were reported in two patients treated with aliskiren in the clinical trials. One of these patients did have predisposing causes for seizures and had a negative electroencephalogram (EEG) and cerebral imaging following the seizures (for the other patient EEG and imaging results were not reported.) Aliskiren was discontinued and there was no re-challenge.

The following adverse events occurred in placebo-controlled clinical trials at an incidence of more than 1% of patients treated with aliskiren, but also occurred at about the same or greater incidence in patients receiving placebo: headache, nasopharyngitis, dizziness, fatigue, upper respiratory tract infection, back pain and cough.

Clinical Laboratory Findings

In controlled clinical trials, clinically relevant changes in standard laboratory parameters were rarely associated with the administration of Tekturna. In multiple-dose studies in hypertensive patients Tekturna had no clinically important effects on total cholesterol, HDL, fasting triglycerides, fasting glucose, or uric acid.

Blood Urea Nitrogen, Creatinine
Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 7% of patients with essential hypertension treated with Tekturna alone vs. 6% on placebo.

Hemoglobin and Hematocrit
Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.08 g/dL and 0.16 volume percent, respectively, for all aliskiren monotherapy) were observed. The decreases were dose-related and were 0.24 g/dL and 0.79 volume percent for 600 mg daily. This effect is also seen with other agents acting on the renin angiotensin system, such as angiotensin inhibitors and angiotensin receptor blockers, and may be mediated by reduction of angiotensin II which stimulates erythropoietin production via the AT1 receptor. These decreases led to slight increases in rates of anemia with aliskiren compared to placebo were observed (0.1% for any aliskiren use, 0.3% for aliskiren 600 mg daily, vs. 0% for placebo). No patients discontinued therapy due to anemia.

Serum Potassium
Increases in serum potassium >5.5 meq/L were infrequent in patients with essential hypertension treated with Tekturna alone (0.9% compared to 0.6% with placebo). However, when used in combination with an angiotensin-converting enzyme inhibitor (ACEI) in a diabetic population increases in serum potassium were more frequent (5.5%) and routine monitoring of electrolytes and renal function is indicated in this population.

Serum Uric Acid
Aliskiren monotherapy produced small median increases in serum uric acid levels (about 6 µmol/L) while HCTZ produced larger increases (about 30 µmol/L). The combination of aliskiren with HCTZ appears to be additive (about a 40 µmol/L increase). The increases in uric acid appear to lead to slight increases in uric acid-related AEs: elevated uric acid (0.4% vs. 0.1%), gout (0.2% vs. 0.1%), and renal stones (0.2% vs. 0%).

Creatine Kinase
Increases in creatine kinase of >300% were recorded in about 1% of aliskiren monotherapy patients vs. 0.5% of placebo patients. Five cases of creatine kinase rises, three leading to discontinuation and one diagnosed as subclinical rhabdomyolysis and another as myositis, were reported as adverse events with aliskiren use in the clinical trials. No cases were associated with renal dysfunction.

OVERDOSAGE
Limited data are available related to overdosage in humans. The most likely manifestation of overdosage would be hypotension. If symptomatic hypotension should occur, supportive treatment should be initiated.

DOSAGE AND ADMINISTRATION
The usual recommended starting dose of Tekturna® (aliskiren) is 150 mg once daily. In patients whose blood pressure is not adequately controlled, the daily dose may be increased to 300 mg. Doses above 300 mg did not give an increased blood pressure response but increased the rate of diarrhea. The antihypertensive effect of a given dose is substantially attained (85%-90%) by 2 weeks.

Tekturna may be administered with other antihypertensive agents. Most exposure to date is with diuretics and an angiotensin receptor blocker (valsartan) and the drugs together have a greater effect at

their maximum recommended doses than either drug alone. It is not known whether additive effects are present when aliskiren is used with angiotensin-converting enzyme inhibitors or beta blockers.

No initial dosage adjustment is required in elderly patients, for patients with mild-to-severe renal impairment, or for patients with mild-to-severe hepatic insufficiency. Care should be exercised when dosing Tekturna in patients with severe renal impairment, as clinical experience with such patients is limited.

Patients should establish a routine pattern for taking Tekturna with regard to meals. High fat meals decrease absorption substantially (see Absorption and Distribution).

HOW SUPPLIED

Tekturna® (aliskiren) is supplied as a light-pink, biconvex unscored round tablet containing 150 mg of aliskiren, and as a light-red biconvex ovaloid tablet containing 300 mg of aliskiren. Tablets are imprinted with NVR on one side and IL, IU, on the other side of the 150, and 300 mg tablets, respectively.

All strengths are packaged in bottles and unit-dose blister packages (10 strips of 10 tablets) as described below in Table 4.

Table 4: Tekturna Tablets Supply

Tablet	Color	Imprint	Imprint	NDC 0078-XXXX-XX		
		Side 1	Side 2	Bottle of 30	Bottle of 90	Blister Packages of 100
150 mg	Light-pink	NVR	IL	0485-15	0485-34	0485-35
300 mg	Light-red	NVR	IU	0486-15	0486-34	0486-35

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Protect from moisture.

Dispense in tight container (USP).

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PATIENT INFORMATION

T2007-06

TEKTURNA® (PRONOUNCED TEK-TURN-A)
(aliskiren)
Tablets

Dosing Strengths:
150 mg tablets
300 mg tablets

Available by Prescription Only

Please read all of the available information before you start taking Tekturna. This leaflet does not take the place of talking with your doctor about your condition and treatment. If you have any questions about Tekturna, ask your doctor or pharmacist, visit www.Tekturna.com, or call 1-888-Tekturna (1-888-835-8876).

IMPORTANT WARNING: If you get pregnant, stop taking Tekturna and call your doctor right away. Tekturna may harm an unborn baby, causing injury and even death. If you plan to become pregnant, talk to your doctor about other treatment options before taking Tekturna.

What Is High Blood Pressure (Hypertension)?
Blood pressure is the force that pushes the blood through your blood vessels to all the organs of your body. You have high blood pressure when the force of your blood moving through your blood vessels is too great. Renin (pronounced REE-nin) is a chemical in the body that starts a process that makes blood vessels narrow, leading to high blood pressure.

High blood pressure makes the heart work harder to pump blood throughout the body and causes damage to the blood vessels. If high blood pressure is not treated, it can lead to stroke, heart attack, heart failure, kidney failure, and vision problems.

What Is Tekturna?
Tekturna is a type of prescription medicine called a direct renin inhibitor that works in the body to help lower blood pressure (hypertension).

How Does Tekturna Work?
Tekturna reduces the effect of renin and the harmful process that narrows blood vessels. Tekturna helps blood vessels relax and widen so blood pressure is lowered.

Who Should Not Take Tekturna?
- **If you get pregnant, stop taking Tekturna and call your doctor right away. If you plan to become pregnant, talk to your doctor about other treatment options for your high blood pressure.**
- **Do not take Tekturna if you are allergic to any of its ingredients.**

Aliskiren is the active ingredient in Tekturna. The inactive ingredients (the ingredients that bind the tablet together) are colloidal silicon dioxide, crospovidone, hypromellose, iron oxide colorants, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, and titanium dioxide. These inactive ingredients are considered safe and are commonly used in many medications. Talk to your doctor if you have questions.

Tekturna has not been studied in children under 18 years of age.

What Should I Tell My Doctor Before Taking Tekturna?

Tell your doctor about all your medical conditions, including whether you:

- are pregnant or planning to become pregnant.
- are breast-feeding. It is not known if Tekturna passes into your breast milk. You should choose either to take Tekturna or breast-feed, but not both.
- have kidney problems.
- are allergic to any of the ingredients in Tekturna.

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. Especially tell your doctor if you are taking:

- other medicines for high blood pressure or a heart problem.
- water pills (also called "diuretics").
- medicines for treating fungus or fungal infections.

Your doctor or pharmacist will know what medicines are safe to take together.

How Should I Take Tekturna?

- Take Tekturna once a day, at the same time each day. As with any blood pressure medication, it is important to take Tekturna on a regular daily basis exactly as prescribed by your doctor.
- Tekturna can be taken by itself or safely in combination with other medicines to lower high blood pressure. It can also be safely taken in combination with medications for other conditions such as high cholesterol or diabetes. Your doctor may change your dose if needed.
- Tekturna can be taken with or without food.

If you miss a dose, take it as soon as you remember. If it is close to your next dose, do not take the missed dose. Just take the next dose at your regular time. If you take too much Tekturna, call your doctor or Poison Control Center, or go to the nearest hospital emergency room.

What Are Possible Side Effects Of Tekturna?

Tekturna may cause the following serious side effect:

- **Low blood pressure (hypotension).** Your blood pressure may get too low if you also take water pills, are on a low-salt diet, get dialysis treatments, have heart problems, or get sick with vomiting or diarrhea. Lie down if you feel faint or dizzy. Call your doctor right away.

Side effects were usually mild and brief. Few patients decided to stop taking Tekturna because of side effects. In clinical studies, the most common side effect experienced by more patients taking Tekturna than patients taking a sugar pill (placebo) was diarrhea. Other less common reactions to Tekturna include cough, and rash.

If you develop an allergic reaction involving swelling of the face, lips, throat and/or tongue which may cause difficulty in breathing and swallowing, stop taking Tekturna and contact your doctor immediately.

For a complete list of side effects, ask your doctor or pharmacist. Tell your doctor if you get any side effect that bothers you or will not go away.

How Do I Store Tekturna?

- Store Tekturna tablets at room temperature between 59° to 86°F.
- Keep Tekturna in the original prescription bottle in a dry place. Do not remove the desiccant (drying agent) from the bottle.
- Keep Tekturna and all medicines out of the reach of children.

General Information About Tekturna

Do not give Tekturna to other people, even if they have the same condition or symptoms you have. It may harm them.

This leaflet summarizes the most important information about Tekturna.

For more information about Tekturna, ask your doctor or pharmacist, visit www.Tekturna.com, or call 1-888-Tekturna (1-888-835-8876).

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/s/

Robert Temple
3/5/2007 04:57:53 PM

APPENDIX D

US005559111A

United States Patent [19]

Göschke et al.

[11] **Patent Number: 5,559,111**

[45] **Date of Patent: Sep. 24, 1996**

[54] **δ-AMINO-γ-HYDROXY-ω-ARYL-ALKANOIC ACID AMIDES**

[75] Inventors: **Richard Göschke**, Bottmingen, Switzerland; **Jürgen K. Maibaum**, Weil-Haltingen, Germany; **Walter Schilling**, Himmelried; **Stefan Stutz**, Basel, bpth of, Switzerland; **Pascal Rigollier**, Sierentz, France; **Yasuchika Yamaguchi**, Basel, Switzerland; **Nissim C. Cohen**, Village-Neuf, France; **Peter Herold**, Arlesheim, Switzerland

[73] Assignee: **Ciba-Geigy Corporation**, Tarrytown, N.Y.

[21] Appl. No.: **416,242**

[22] Filed: **Apr. 4, 1995**

[30] **Foreign Application Priority Data**

Apr. 18, 1994 [CH] Switzerland 1169/94

[51] **Int. Cl.**[6] **A61K 31/165**; A61K 31/54; C07D 237/20; C07D 294/14

[52] **U.S. Cl.** **514/227.5**; 514/620; 544/58.1; 544/168; 544/316; 546/216; 546/226; 546/233; 546/237; 548/131; 548/187; 548/204; 548/232; 548/253; 548/319.5; 548/338.1; 548/546; 548/550; 554/36; 554/37; 554/42; 554/45

[58] **Field of Search** 554/55, 60; 514/227.5

[56] **References Cited**

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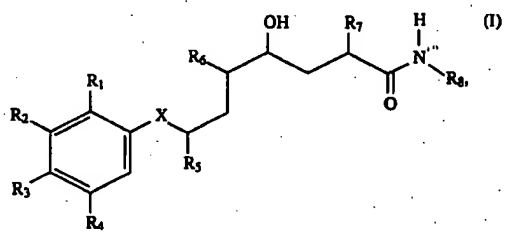
Primary Examiner—Robert W. Ramsuer

Attorney, Agent, or Firm—Marla J. Mathias; Irving M. Fishman; Karen G. Kaiser

[57] **ABSTRACT**

δ-Amino-γ-hydroxy-ω-aryl-alkanoic acid amides of formula I



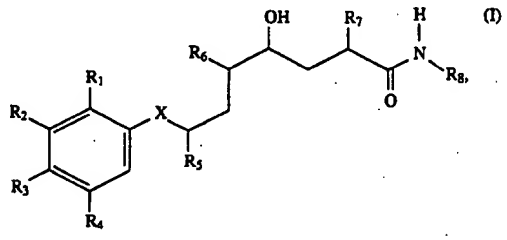
(I)

and the salts thereof, have renin-inhibiting properties and can be used as antihypertensive medicinal active ingredients.

24 Claims, No Drawings

δ-AMINO-γ-HYDROXY-ω-ARYL-ALKANOIC ACID AMIDES

The invention relates to novel δ-amino-γ-hydroxy-ω-aryl-alkanoic acid amides of formula I



(I)

wherein

R_1 is hydrogen, hydroxy, lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy or free or esterified or amidareal carboxy-lower alkoxy,

R_2 is hydrogen, lower alkyl, cycloalkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, hydroxy, optionally lower alkanoylated, halogenated or sulfonylated hydroxy-lower alkoxy; amino-lower alkyl that is unsubstituted or substituted by lower alkyl, by lower alkanoyl and/or by lower alkoxycarbonyl; optionally hydrogenated heteroaryl-lower alkyl; amino-lower alkoxy that is substituted by lower alkyl, by lower alkanoyl and/or by lower alkoxycarbonyl; oxo-lower alkoxy, lower alkoxy, cycloalkoxy, lower alkenyloxy, cycloalkoxy-lower alkoxy, lower alkoxy-lower alkoxy, lower alkoxy-lower alkenyl, lower alkenyloxy-lower alkoxy, lower alkoxy-lower alkenyloxy, lower alkenyloxy-lower alkyl, lower alkanoyl-lower alkoxy, optionally S-oxidised lower alkylthio-lower alkoxy, lower alkylthio-(hydroxy)-lower alkoxy, aryl-lower alkoxy, optionally hydrogenated heteroaryl-lower alkoxy, cyano-lower alkoxy, free or esterified or amidated carboxy-lower alkoxy or free or esterified or amidated carboxy-lower alkyl,

R_3 is optionally halogenated lower alkyl, lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, hydroxy-lower alkyl, optionally S-oxidised lower alkylthio-lower alkyl, optionally hydrogenareal heteroarylthio-lower alkyl, optionally hydrogenated heteroaryl-lower alkyl; amino-lower alkyl that is unsubstituted or N-mono- or N,N-di-lower alkylated, N-lower alkanoylated or N-lower alkanesulfonylated or N,N-disubstituted by lower alkylene, by unsubstituted or N'-lower alkylated or N'-lower alkanoylated aza-lower alkylene, by oxa-lower alkylene or by optionally S-oxidised thia-lower alkylene; cyano-lower alkyl, free or esterified or amidated carboxy-lower alkyl, cycloalkyl, aryl, hydroxy, lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy, cycloalkoxy-lower alkoxy, hydroxy-lower alkoxy, aryl-lower alkoxy, optionally halogenated lower alkoxy, optionally S-oxidised lower alkylthio-lower alkoxy, optionally hydrogenated heteroaryl-lower alkoxy, optionally hydrogenated heteroarylthio-lower alkoxy; amino-lower alkoxy that is unsubstituted or N-mono- or N,N-di-lower alkylated, N-lower alkanoylated or N-lower alkanesulfonylated or substituted by lower alkylene, by unsubstituted or N'-lower alkylated or N'-lower alkanoylated aza-lower alkylene, by oxa-lower alkylene or by optionally S-oxidised thia-lower alkylene; cyano-lower alkoxy or free or esterified or amidated carboxy lower alkoxy, or together with R_4 is

lower alkylenedioxy or a fused-on benzo or cyclohexeno ring,

R_4 together with R_3 is lower alkylenedioxy or a fused-on benzo or cyclohexeno ring, or is hydrogen, lower alkyl, hydroxy, lower alkoxy or cycloalkoxy,

X is methylene or hydroxymethylene,

R_5 is lower alkyl or cycloalkyl,

R_6 is unsubstituted or N-mono- or N,N-di-lower alkylated or N-lower alkanoylated amino,

R_7 is lower alkyl, lower alkenyl, cycloalkyl or aryl-lower alkyl, and

R_8 is lower alkyl, cycloalkyl, free or aliphatically esterideal or etherideal hydroxy-lower alkyl; amino-lower alkyl that is unsubstituted or N-lower alkanoylated or N-mono- or N,N-di-lower alkylated or N,N-disubstituted by lower alkylene, by hydroxy-, lower alkoxy- or lower alkanoyloxy-lower alkylene, by unsubstituted or N'-lower alkanoylated or N'-lower alkylated aza-lower alkylene, by oxa-lower alkylene or by optionally S-oxidised thia-lower alkylene; free or esterified or amidated carboxy-lower alkyl, free or esterified or amidated dicarboxy-lower alkyl, free or esterideal or amidated carboxy-(hydroxy)-lower alkyl, free or esterified or amidated carboxycycloalkyl-lower alkyl, cyano-lower alkyl, lower alkanesulfonyl-lower alkyl, unsubstituted or N-mono- or N,N-di-lower alkylated thiocarbamoyl-lower alkyl, unsubstituted or N-mono- or N,N-di-lower alkylated sulfamoyl-lower alkyl, or a heteroaryl radical bonded via a carbon atom and optionally hydrogenated and/or oxo-substituted, or lower alkyl substituted by a heteroaryl radical bonded via a carbon atom and optionally hydrogenated and/or oxo-substituted,

and to the salts thereof, to processes for the preparation of the compounds according to the invention, to pharmaceutical compositions containing them, and to their use as medicinal active ingredients.

Aryl and aryl in aryl-lower alkoxy, aryl-lower alkyl and the like is, for example, phenyl or naphthyl that is unsubstituted or mono-, di- or tri-substituted by lower alkyl, lower alkoxy, hydroxy, lower alkylamino, di-lower alkylamino, halogen and/or by trifluoromethyl.

Cycloalkoxy and cycloalkoxy in cycloalkoxy-lower alkoxy is, for example, 3- to 8-membered, preferably 3-, 5- or 6-membered, cycloalkoxy, such as cyclopropyloxy, cyclopentyloxy, cyclohexyloxy, also cyclobutyloxy, cycloheptyloxy or cyclooctyloxy.

Cycloalkyl is, for example, 3- to 8-membered, preferably 3-, 5- or 6-membered, cycloalkyl, such as cyclopropyl, cyclopentyl, cyclohexyl, also cyclobutyl, cycloheptyl or cyclooctyl.

Free or esterified or amidated carboxy-lower alkoxy is, for example, carboxy-lower alkoxy, lower alkoxycarbonyl-lower alkoxy, carbamoyl-lower alkoxy or N-mono- or N,N-di-lower alkylcarbamoyl-lower alkoxy.

Optionally lower alkanoylated, halogenated or sulfonylated hydroxy-lower alkoxy is, for example, lower alkanoyloxy-lower alkyl, hydroxy-lower alkoxy, halo-(hydroxy)-lower alkoxy or lower alkanesulfonyl-(hydroxy)-lower alkoxy.

Amino-lower alkyl that is unsubstituted or substituted by lower alkyl, lower alkanoyl and/or by lower alkoxycarbonyl is, for example, amino-lower alkyl, lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl, lower alkanoylamino-lower alkyl or lower alkoxycarbonylamino-lower alkyl.

Amino-lower alkoxy that is unsubstituted or substituted by lower alkyl, lower alkanoyl and/or by lower alkoxycarbonyl is, for example, amino-lower alkoxy, lower alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy, lower alkanoylamino-lower alkoxy or lower alkoxycarbonylamino-lower alkoxy.

Optionally S-oxidised lower alkylthio-lower alkoxy is, for example, lower alkylthio-lower alkoxy or lower alkanesulfonyl-lower alkoxy.

Optionally hydrogenated heteroaryl-lower alkoxy is, for example, optionally partially hydrogenated or N-oxidised pyridyl-lower alkoxy, thiazolyl-lower alkoxy or especially morpholino-lower alkoxy.

Optionally hydrogenated heteroarylthio-lower alkoxy is, for example, optionally partially or fully hydrogenareal heteroarylthio-lower alkoxy, such as thiazolylthio-lower alkoxy or thiazolinylthio-lower alkoxy, imidazolylthio-lower alkoxy, optionally N-oxidised pyridylthio-lower alkoxy or pyrimidinylthio-lower alkoxy.

Free or esterified or amidated carboxy-lower alkyl is, for example, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, carbamoyl-lower alkyl or N-mono- or N,N-di-lower alkylcarbamoyl-lower alkyl.

Optionally halogenated lower alkyl is, for example, lower alkyl or polyhalo-lower alkyl.

Optionally halogenated lower alkoxy is, for example, lower alkoxy or polyhalo-lower alkoxy.

Optionally S-oxidised lower alkylthio-lower alkyl is, for example, lower alkylthio-lower alkyl or lower alkanesulfonyl-lower alkyl.

Optionally S-oxidised lower alkylthio-lower alkoxy is, for example, lower alkylthio-lower alkoxy or lower alkanesulfonyl-lower alkoxy.

Optionally hydrogenated heteroaryl-lower alkyl is, for example, optionally partially hydrogenated or N-oxidised pyridyl-lower alkyl.

Optionally hydrogenated heteroarylthio-lower alkyl is, for example, thiazolylthio-lower alkyl or thiazolinylthio-lower alkyl, imidazolylthio-lower alkyl, optionally N-oxidised pyridylthio-lower alkyl or pyrimidinylthio-lower alkyl.

Amino-lower alkyl that is unsubstituted or N-mono- or N,N-di-lower alkylated, N-lower alkanoylated or N-lower alkanesulfonylated or N,N-disubstituted by lower alkylene, by unsubstituted or N'-lower alkylated or N'-lower alkanoylated aza-lower alkylene, by oxa-lower alkylene or by optionally S-oxidised thia-lower alkylene is, for example, amino-lower alkyl, lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl, lower alkanoylamino-lower alkyl, lower alkanesulfonylamino-lower alkyl, polyhalo-lower alkanesulfonylamino-lower alkyl, pyrrolidino-lower alkyl, piperidino-lower alkyl, piperazino-, N'-lower alkylpiperazino- or N'-lower alkanoylpiperazino-lower alkyl, morpholino-lower alkyl, thiomorpholino-, S-oxothiomorpholino- or S,S-dioxothiomorpholino-lower alkyl.

Optionally S-oxidised lower alkylthio-lower alkoxy is, for example, lower alkylthio-lower alkoxy or lower alkanesulfonyl-lower alkoxy.

Amino-lower alkoxy that is unsubstituted or N-mono- or N,N-di-lower alkylated, N-lower alkanoylated or N-lower alkanesulfonylated or N,N-disubstituted by lower alkylene, by unsubstituted or N'-lower alkylated or N'-lower alkanoylated aza-lower alkylene, by oxa-lower alkylene or by optionally S-oxidised thia-lower alkylene is, for example, amino-lower alkoxy, lower alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy, lower alkanoylamino-lower alkoxy, lower alkanesulfonylamino-lower alkoxy, polyhalo-lower alkanesulfonylamino-lower alkoxy, pyrrolidino-lower alkoxy, piperidino-lower alkoxy, piperazino-, N'-lower alkylpiperazino- or N'-lower alkanoylpiperazino-lower alkoxy, morpholino-lower alkoxy, thiomorpholino-, S-oxothiomorpholino- or S,S-dioxothio-morpholino-lower alkoxy.

Unsubstituted or N-mono- or N,N-di-lower alkylated or N-lower alkanoylated amino is, for example, amino, lower alkylamino, di-lower alkylamino or lower alkanoylamino.

Free or aliphatically esterified or etherified hydroxy-lower alkyl is, for example, hydroxy-lower alkyl, lower alkanoyloxy-lower alkyl, lower alkoxy-lower alkyl or lower alkenyloxy-lower alkyl.

Amino-lower alkyl that is unsubstituted or N-lower alkanoylated, N-mono- or N,N-di-lower alkylated or N,N-disubstituted by lower alkylene, by hydroxy-, lower alkoxy- or lower alkanoyloxy-lower alkylene, by unsubstituted or N'-lower alkanoylated aza-lower alkylene, by oxa-lower alkylene or by optionally S-oxidised thia-lower alkylene is, for example, amino-lower alkyl, lower alkanoylamino-lower alkyl, N-mono- or N,N-di-lower alkylamino-lower alkyl, optionally hydroxylated or lower alkoxylated piperidino-lower alkyl, such as piperidino-lower alkyl, hydroxypiperidino-lower alkyl or lower alkoxy-piperidino-lower alkyl, piperazino-, W-lower alkylpiperazino- or N'-lower alkanoyl-piperazino-lower alkyl, unsubstituted or lower alkylated morpholino-lower alkyl, such as morpholino-lower alkyl or dimethylmorpholino-lower alkyl, or optionally S-oxidised thio-morpholino-lower alkyl, such as thiomorpholino-lower alkyl or S,S-dioxothiomorpholino-lower alkyl.

Free or esterified or amidated dicarboxy-lower alkyl is, for example, dicarboxy-lower alkyl, di-lower alkoxycarbonyl-lower alkyl, dicarbamoyl-lower alkyl or di-(N-mono- or N,N-di-lower alkylcarbamoyl)-lower alkyl.

Free or esterified or amidated carboxy-(hydroxy)-lower alkyl is, for example, carboxy-(hydroxy)-lower alkyl, lower alkoxycarbonyl-(hydroxy)-lower alkyl or carbamoyl-(hydroxy)-lower alkyl.

Free or esterified or amidated carboxycycloalkyl-lower alkyl is, for example, 5- or 6-membered carboxycycloalkyl-lower alkyl, lower alkoxycarbonylcycloalkyl-lower alkyl, carbamoylcycloalkyl-lower alkyl, or N-mono- or N,N-di-lower alkylcarbamoylcyclo-alkyl-lower alkyl.

Unsubstituted or N-mono- or N,N-di-lower alkylated sulfamoyl-lower alkyl is, for example, sulfamoyl-lower alkyl, lower alkylsulfamoyl-lower alkyl or di-lower alkyl-sulfamoyl-lower alkyl.

Unsubstituted or N-mono- or N,N-di-lower alkylated thiocarbamoyl-lower alkyl is, for example, thiocarbamoyl-lower alkyl, lower alkylthiocarbamoyl-lower alkyl or di-lower alkylthiocarbamoyl-lower alkyl, such as N,N-dimethylthiocarbamoylmethyl.

Heteroaryl that is optionally oxo-substituted, bonded via a carbon atom and optionally hydrogenated, and such a heteroaryl in a lower alkyl that is substituted by heteroaryl radicals that are optionally oxo-substituted, bonded via a carbon atom and optionally hydrogenated, contains as optionally hydrogenated heteroaryl radical, for example, an optionally partially hydrogenated and/or benzo-fused 5-membered aza-, diaza-, triaza-, oxadiaza- or tetraaza-aryl radical or a 6-membered aza- or diaza-aryl radical, and as lower alkyl radical, for example, C_1–C_7alkyl, preferably C_1–C_4alkyl, and is, for example, pyrrolidinyl-lower alkyl, e.g. oxopyrrolidinyl-C_1–C_4alkyl, imidazolyl-lower alkyl, e.g. imidazol-4-yl-C_1–C_4alkyl, benzimidazolyl-lower alkyl, e.g. benzimidazol-2-yl-C_1–C_4alkyl, oxodiazolyl-lower alkyl, e.g. 1,2,4-oxadiazol-5-yl-C_1–C_4alkyl, pyridyl-lower alkyl, e.g. pyridin-2-yl-C_1–C_4alkyl, oxopiperidinyl-

C_1–C_4alkyl, dioxopiperidinyl-C_1–C_4alkyl, oxothiazolyl-C_1–C_4alkyl, oxo-oxazolinyl-C_1–C_4alkyl or quinolinyl-lower alkyl, e.g. quinolin- 2-yl-C_1–C_4alkyl, also morpholinocarbonyl-lower alkyl or unsubstituted or N-lower alkanoylated piperidyl-lower alkyl.

Hereinbefore and hereinafter, lower radicals and compounds are to be understood as being, for example, those having up to and including 7, preferably up to and including 4, carbon atoms.

5- or 6-Membered carboxycycloalkyl-lower alkyl, lower alkoxycarbonylcycloalkyl-lower alkyl, carbamoylcycloalkyl-lower alkyl, N-mono- or N,N-di-lower alkylcarbamoylcyclo-alkyl-lower alkyl is, for example, ω-(1-carboxycycloalkyl)-C_1–C_4alkyl, ω-(1-lower alkoxycarbonylcycloalkyl)-C_1–C_4alkyl, ω-(1-carbamoylcycloalkyl)-C_1–C_4alkyl, ω-(1-lower alkylcarbamoylcycloalkyl)-C_1–C_4alkyl or ω-(1-di-lower alkylcarbamoylcycloalkyl)-C_1–C_4alkyl, wherein cycloalkyl is, for example, cyclopentyl or cyclohexyl, lower alkoxycarbonyl is, for example, C_1–C_4alkoxycarbonyl, such as methoxy- or ethoxycarbonyl, lower alkylcarbamoyl is, for example, C_1–C_4alkylcarbamoyl, such as methylcarbamoyl, di-lower alkylcarbamoyl is, for example, di-C_1–C_4alkylcarbamoyl, such as dimethylcarbamoyl, and lower alkyl is, for example, C_1–C_4alkyl, such as methyl, ethyl, propyl or butyl, especially (1-carboxycyclopentyl)methyl.

5- or 6-Membered cycloalkoxy-lower alkoxy is, for example, cyclopentyloxy- or cyclohexyloxy-C_1–C_4alkoxy, such as cyclopentyloxy- or cyclohexyloxy-methoxy, 2-cyclopentyloxy- or 2-cyclohexyloxy-ethoxy, 2- or 3-cyclopentyloxy- or 2- or 3-cyclohexyloxy-propyloxy or 4-cyclopentyloxy- or 4-cyclohexyloxy-butyloxy, especially cyclopentyloxy- or cyclohexyloxy-methoxy.

5- or 6-Membered cycloalkoxy-lower alkyl is, for example, cyclopentyloxy- or cyclohexyloxy-C_1–C_4alkyl, such as cyclopentyloxy- or cyclohexyloxy-methyl, 2-cyclopentyloxy- or 2-cyclohexyloxy-ethyl, 2- or 3-cyclopentyloxy- or 2- or 3-cyclohexyloxy-propyl, 2-cyclopentyloxy- or 2-cyclohexyloxy-2-methyl-propyl, 2-cyclopentyloxy- or 2-cyclohexyloxy- 2-ethyl-butyl or 4-cyclopentyloxy- or 4-cyclohexyloxy-butyl, especially cyclopentyloxy- or cyclohexyloxy-methyl.

Amino-lower alkoxy is, for example, amino-C_1–C_4alkoxy, such as 2-aminoethoxy or 5-aminopentyloxy, also 3-aminopropyloxy or 4-aminobutyloxy.

Amino-lower alkyl is, for example, amino-C_1–C_4alkyl, such as 2-aminoethyl, 3-aminopropyl or 4-aminobutyl.

Carbamoyl-(hydroxy)-lower alkyl is, for example, carbamoyl-C_1–C_7(hydroxy)alkyl, such as 1-carbamoyl-2-hydroxyethyl.

Carbamoyl-lower alkoxy is, for example, carbamoyl-C_1–C_4alkoxy, such as carbamoylmethoxy, 2-carbamoylethoxy, 3-carbamoylpropyloxy or 4-carbamoylbutyloxy, especially carbamoylmethoxy.

Carbamoyl-lower alkyl is, for example, carbamoyl-C_1–C_7alkyl, such as carbamoylmethyl, 2-carbamoylethyl, 3-carbamoylpropyl, 2-(3-carbamoyl)propyl, 2-carbamoylpropyl, 3-(1-carbamoyl)propyl, 2-(2-carbamoyl)propyl, 2-(carbamoyl-2-methyl)propyl, 4-carbamoylbutyl, 1-carbamoylbutyl, 1-(1-carbamoyl-2-methyl)butyl or 3-(4-carbamoyl- 2-methyl)butyl.

Carboxy-(hydroxy)-lower alkyl is, for example, carboxy-C_1–C_7(hydroxy)alkyl, such as 1 -carboxy-2-hydroxy-ethyl.

Carboxy-lower alkoxy is, for example, carboxy-C_1–C_4alkoxy, such as carboxymethoxy, 2-carboxyethoxy, 2- or 3-carboxypropyloxy or 4-carboxybutyloxy, especially carboxy-methoxy.

Carboxy-lower alkyl is, for example, carboxy-C_1–C_4alkyl, such as carboxymethyl, 2-carboxyethyl, 2- or 3-carboxypropyl, 2-carboxy-2-methyl-propyl, 2-carboxy-2-ethyl-butyl or 4-carboxybutyl, especially carboxymethyl.

Cyano-lower alkoxy is, for example, cyano-C_1–C_4alkoxy, such as cyanomethoxy, 2-cyano-ethoxy, 2- or 3-cyanopropyloxy or 4-cyanobutyloxy, especially cyanomethoxy.

Cyano-lower alkyl is, for example, cyano-C_1–C_4alkyl, such as cyanomethyl, 2-cyanoethyl, 2- or 3-cyanopropyl, 2-cyano-2-methyl-propyl, 2-cyano-2-ethyl-butyl or 4-cyanobutyl, especially cyanomethyl.

Di-(N-mono- or N,N-di-lower alkylcarbamoyl)-lower alkyl is, for example, di-(N-mono- or N,N-di-C_1–C_4alkylcarbamoyl)-C_1–C_4alkyl, such as 1,2-di-(N-mono- or N,N-di-C_1–C_4alkylcarbamoyl)ethyl or 1,3-di-(N-mono- or N,N-di-C_1–C_4alkylcarbamoyl)propyl.

Dicarbamoyl-lower alkyl is, for example, dicarbamoyl-C_1–C_4alkyl, such as 1,2-dicarbamoylethyl or 1,3-dicarbamoylpropyl.

Dicarboxy-lower alkyl is, for example, dicarboxy-C_1–C_4alkyl, such as 1,2-dicarboxyethyl or 1,3-dicarboxypropyl.

Dimethylmorpholino-lower alkoxy can be N-oxidised and is, for example, 2,6-dimethylmorpholino- or 3,5-dimethylmorpholino-C_1–C_4alkoxy, such as 2,6-dimethylmorpholino- or 3,5-dimethylmorpholino-methoxy, 2-(2,6-dimethylmorpholino-or 3,5-dimethylmorpholino)-ethoxy, 3-(2,6-dimethylmorpholino-or 3,5-dimethylmorpholino)-propyloxy, 2-(2,6-dimethylmorpholino- or 3,5-dimethylmorpholino-3-methyl)propyloxy, or 1- or 2-[4-(2,6-dimethylmorpholino- or 3,5-dimethylmorpholino)]-butyloxy.

Dimethylmorpholino-lower alkyl can be N-oxidised and is, for example, 2,6-dimethylmorpholino- or 3,5-dimethylmorpholino-C_1–C_4alkyl, such as 2,6-dimethylmorpholino- or 3,5-dimethylmorpholino-methoxy, 2-(2,6-dimethylmorpholino- or 3,5-dimethylmorpholino)-ethoxy, 3-(2,6-dimethylmorpholino- or 3,5-dimethylmorpholino)-propyl, 2-(2,6-dimethylmorpholino- or 3,5-dimethylmorpholino-3-methyl)-propyl, or 1- or 2-[4-(2,6-dimethylmorpholino- or 3,5-dimethylmorpholino)]-butyl.

Di-lower alkoxycarbonyl-lower alkyl is, for example, di-lower alkoxycarbonyl-C_1–C_4alkyl, such as 1,2-dimethoxycarbonylethyl, 1,3-dimethoxycarbonylpropyl, 1,2-dimethoxycarbonylethyl or 1,3-diethoxycarbonylpropyl.

Di-lower alkylamino is, for example, di-C_1–C_4alkylamino, such as dimethylamino, N-methyl-N-ethylamino, diethylamino, N-methyl-N-propylamino or N-butyl-N-methylamino.

Di-lower alkylamino-lower alkoxy is, for example, N,N-di-C_1–C_4alkylamino-C_1–C_4alkoxy, such as 2-dimethylaminoethoxy, 3-dimethylaminopropyloxy, 4-dimethylaminobutyloxy, 2-diethylaminoethoxy, 2-(N-methyl-N-ethylamino)ethoxy or 2-(N-butyl-N-methyl-amino)ethoxy.

Di-lower alkylamino-lower alkyl is, for example, N,N-di-C_1–C_4alkylamino-C_1–C_4alkyl, such as 2-dimethylaminoethyl, 3-dimethylaminopropyl, 4-dimethylaminobutyl, 2-diethylaminoethyl, 2-(N-methyl-N-ethyl-amino)ethyl or 2-(N-butyl-N-methyl-amino)ethyl.

Di-lower alkylcarbamoyl-lower alkoxy is, for example, N,N-di-C_1–C_4alkylcarbamoyl-C_1–C_4alkoxy, such as methyl- or dimethyl-carbamoyl-C_1–C_4alkoxy, such as N-methyl-, N-butyl- or N,N-dimethyl-carbamoylmethoxy, 2-(N-methylcarbamoyl)ethoxy, 2-(N-butylcarbamoyl)ethoxy, 2-(N,N-dimethylcarbamoyl)ethoxy, 3-(N-methylcarbamoyl)propyloxy, 3-(N-butylcarbamoyl)propyloxy, 3-(N,N-dimethylcarbamoyl)propyloxy or 4-(N-methylcar-

bamoyl)butyloxy, 4-(N-butylcarbamoyl)butyloxy or 4-(N, N-dimethylcarbamoyl)butyloxy, especially N-methyl-, N-butyl- or N,N-dimethyl-carbamoylmethoxy.

Di-lower alkylcarbamoyl-lower alkyl is, for example, N,N-di-C_1–C_4alkylcarbamoyl-C_1–C_4alkyl, such as 2-dimethylcarbamoylethyl, 3-dimethylcarbamoylpropyl, 2-dimethylcarbamoylpropyl, 2-(dimethylcarbamoyl-2-methyl) propyl or 2-(1-dimethylcarbamoyl- 3-methyl)butyl.

Di-lower alkylsulfamoyl-lower alkyl is, for example, N,N-di-C_1–C_4alkylsulfamoyl-C_1–C_4alkyl, N,N-dimethylsulfamoyl-C_1–C_4alkyl, such as N,N-dimethylsulfamoylmethyl, 2-(N,N-dimethylcarbamoyl)ethyl, 3-(N,N-dimethylcarbamoyl)propyl or 4-(N,N-dimethylcarbamoyl)butyl, especially N,N-dimethylcarbamoylmethyl.

Unsubstituted or N-lower alkanoylated piperidyl-lower alkyl is, for example, 1-C_1–C_7-lower alkanoylpiperidin-4-yl-C_1–C_4alkyl, such as 1-acetylpiperidinylmethyl or 2-(1-acetylpiperidinyl)ethyl.

Optionally partially hydrogenated or N-oxidised pyridyl-lower alkoxy is, for example, optionally partially hydrogenated pyridyl- or N-oxidopyridyl-C_1–C_4alkoxy, such as pyridyl- or N-oxidopyridyl-methoxy, 2-pyridylethoxy, 2- or 3-pyridylpropyloxy or 4-pyridylbutyloxy, especially 3- or 4-pyridylmethoxy.

Optionally partially hydrogenated or N-oxidised pyridyl-lower alkyl is, for example, optionally partially hydrogenated pyridyl- or N-oxidopyridyl-C_1–C_4alkyl, such as pyridyl- or N-oxidopyridyl-methyl, 2-pyridylethyl, 2- or 3-pyridylpropyl or 4-pyridylbutyl, especially 3- or 4-pyridylmethyl.

Halo-(hydroxy)-lower alkoxy is, for example, halo-C_2–C_7(hydroxy)alkoxy, especially halo-C_2–C_4(hydroxy)alkoxy, such as 3-halo-, such as 3-chloro-2-hydroxy-propyloxy.

Hydroxy-lower alkoxy is, for example, hydroxy-C_2–C_7alkoxy, especially hydroxy-C_2–C_4alkoxy, such as 2-hydroxybutyloxy, 3-hydroxypropyloxy or 4-hydroxybutyloxy.

Hydroxy-lower alkyl is, for example, hydroxy-C_2–C_7alkyl, especially hydroxy-C_2–C_4alkyl, such as 2-hydroxyethyl, 3-hydroxypropyl or 4-hydroxybutyl.

Hydroxypiperidino-lower alkyl is, for example, 3- or 4-hydroxypiperidino-C_1–C_4alkoxy, such as 3- or 4-hydroxypiperidinomethoxy, 2-(3- or 4-hydroxypiperidino)ethoxy, 3-(3- or 4-hydroxypiperidino)propyloxy or 4-(3- or 4-hydroxypiperidino)butyloxy.

Imidazolyl-lower alkyl is, for example, imidazolyl-C_1–C_4alkyl, such as imidazol-4-yl-methyl, 2-(imidazol-4-yl)ethyl, 3-(imidazol-4-yl)propyl or 4-(imidazol-4-yl)butyl.

Imidazolyl-lower alkoxy is, for example, imidazolyl-C_1–C_4alkoxy, such as imidazol-4-yl-methoxy, 2-(imidazol-4-yl)ethoxy, 3-(imidazol-4-yl)propyloxy or 4-(imidazol-4-yl)butyloxy.

Imidazolyl-lower alkyl is, for example, imidazolyl-C_1–C_4alkyl, such as imidazol-4-yl-methyl, 2-(imidazol-4-yl)ethyl, 3-(imidazol-4-yl)propyl or 4-(imidazol-4-yl)butyl.

Morpholinocarbonyl-lower alkyl is, for example, morpholinocarbonyl-C_1–C_4alkyl, such as 1-morpholinocarbonylethyl, 3-morpholinocarbonylpropyl, or 1-(morpholinocarbonyl- 2-methyl)propyl.

Morpholino-lower alkoxy can be N-oxidised and is, for example, morpholino-C_1–C_4alkoxy, such as 1-morpholinoethoxy, 3-morpholinopropyloxy, or 1-(morpholino- 2-methyl)propyloxy.

Morpholino-lower alkyl can be N-oxidised and is, for example, morpholino-C_1–C_4alkyl, such as morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl or 1- or 2-(4-morpholino)butyl.

Lower alkanoyl is, for example, C_1–C_7alkanoyl, especially C_2–C_6alkanoyl, such as acetyl, propionyl, butyryl, isobutyryl or pivaloyl.

Lower alkanoylamino is, for example, N-C_1–C_7alkanoylamino, such as acetylamino or pivaloylamino.

Lower alkanoylamino is, for example, N-C_1–C_7alkanoylamino, such as acetylamino or pivaloylamino.

Lower alkanoylamino-lower alkyl is, for example, N-C_1–C_4alkanoylamino-C_1–C_4alkyl, such as 2-acetoxyaminoethyl.

Lower alkanoylamino-lower alkyl is, for example, N-C_1–C_4alkanoylamino-C_1–C_4alkyl, such as 2-acetoxyaminoethyl.

Lower alkanoyl-lower alkoxy (oxo-lower alkoxy) carries the lower alkanoyl group in a position higher than the α-position and is, for example, C_1–C_7alkanoyl-C_1–C_4alkoxy, such as 4-acetylbutoxy.

Lower alkanoyloxy-lower alkyl carries the lower alkanoyloxy group in a position higher than the α-position and is, for example, C_1–C_7alkanoyloxy-C_1–C_4alkyl, such as 4-acetoxy-butyl.

Lower alkanesulfonyl-(hydroxy)-lower alkoxy is, for example, C_1–C_7alkanesulfonyl-C_1–C_4(hydroxy)alkoxy, such as 3-methanesulfonyl-2-hydroxy-propyloxy.

Lower alkanesulfonyl-lower alkoxy is, for example, C_1–C_7alkanesulfonyl-C_1–C_4alkoxy, such as methanesulfonylmethoxy or 3-methanesulfonyl-2-hydroxy-propyloxy.

Lower alkanesulfonylamino-lower alkoxy is, for example, C_1–C_7alkanesulfonylamino-C_1–C_4alkoxy, such as ethanesulfonylaminomethoxy, 2-ethanesulfonylaminoethoxy, 3-ethanesulfonylaminopropyloxy or 3-(1,1-dimethylethanesulfonylamino)propyloxy.

Lower alkanesulfonylamino-lower alkyl is, for example, C_1–C_7alkanesulfonylamino-C_1–C_4alkyl, such as ethanesulfonylaminomethyl, 2-ethanesulfonylaminoethyl, 3-ethanesulfonylaminopropyl or 3-(1,1-dimethylethanesulfonylamino)propyl.

Lower alkanesulfonyl-lower alkyl is, for example, C_1–C_7alkanesulfonyl-C_1–C_4alkyl, such as ethanesulfonylmethyl, 2-ethanesulfonylethyl, 3-ethanesulfonylpropyl or 3-(1,1-dimethylethanesulfonyl)propyl.

Lower alkenyl is, for example, C_1–C_7alkenyl, such as vinyl or allyl.

Lower alkenyloxy is, for example, C_1–C_7alkenyloxy, such as allyloxy.

Lower alkenyloxy-lower alkoxy is, for example, C_1–C_7alkenyloxy-C_1–C_4alkoxy, such as allyloxymethoxy.

Lower alkenyloxy-lower alkyl is, for example, C_1–C_7alkenyloxy-C_1–C_4alkyl, such as allyloxymethyl.

Lower alkoxy is, for example, C_1–C_7alkoxy, preferably C_1–C_5alkoxy, such as methoxy, ethoxy, propyloxy, isopropyloxy, butyloxy, isobutyloxy, secondary butyloxy, tertiary butyloxy, pentyloxy or a hexyloxy or heptyloxy group.

Lower alkoxycarbonyl is, for example, C_1–C_7alkoxycarbonyl, preferably C_1–C_5alkoxycarbonyl, such as methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, isopropyloxycarbonyl, butyloxycarbonyl, isobutyloxycarbonyl, secondary butyloxycarbonyl, tertiary butyloxy, pentyloxycarbonyl or a hexyloxycarbonyl or heptyloxycarbonyl group.

Lower alkoxycarbonyl-(hydroxy)-lower alkyl is, for example, C_1–C_4alkoxycarbonyl-C_1–C_7(hydroxy)alkyl, such as 1-methoxycarbonyl- or 1-ethoxycarbonyl-2-hydroxyethyl.

Lower alkoxycarbonylamino-lower alkoxy is, for example, C_1–C_7alkoxycarbonylamino-C_2–C_7alkoxy, prefer-

ably C_2–C_5alkoxycarbonylamino-C_2–C_7alkoxy, such as methoxycarbonylamino-C_2–C_7alkoxy, ethoxycarbonylamino-C_2–C_7alkoxy, propyloxycarbonylamino-C_2–C_7alkoxy, isobutyloxycarbonylamino-C_2–C_7alkoxy, butyloxycarbonylamino-C_2–C_7alkoxy, isobutyloxycarbonylamino-C_2–C_7alkoxy, secondary butyloxycarbonylamino-C_2–C_7alkoxy or tertiary butyloxyamino-C_2–C_7alkoxy, wherein C_2–C_7alkoxy is, for example, methoxy, ethoxy, propyloxy, butyloxy, pentyloxy or hexyloxy.

Lower alkoxycarbonylamino-lower alkyl is, for example, C_1–C_7alkoxycarbonylamino-C $_2$–C_7alkyl, preferably C_2–C_5alkoxycarbonylamino-C_2–C_7alkyl, such as methoxycarbonyl-C $_2$–C_7alkyl, ethoxycarbonylamino-C_2–C_7-alkyl, propyloxycarbonylamino-C_2–C_7-alkyl isopropyloxycarbonylamino-C_2–C_7alkyl, butyloxycarbonylamino-C_2–C_7alkyl, isobutyloxycarbonylamino-C_2–C_7alkyl, secondary butyloxycarbonylamino-C_2–C_7alkyl or tertiary butyloxyamino-C_2–C_7alkyl, wherein C_2–C_7alkyl is, for example, methyl, ethyl, propyl, butyl, pentyl or hexyl.

Lower alkoxycarbonyl-lower alkoxy is, for example, C_1–C_4alkoxycarbonyl-C_1–C_4alkoxy, such as methoxycarbonyl- or ethoxycarbonyl-methoxy, 2-methoxycarbonyl- or 2-ethoxycarbonyl-ethoxy, 2- or 3-methoxycarbonyl- or 2- or 3-ethoxycarbonyl-propyloxy or 4-methoxycarbonyl- or 4-ethoxycarbonyl-butyloxy, especially methoxycarbonyl- or ethoxycarbonyl-methoxy or 3-methoxycarbonyl- or 3-ethoxycarbonyl-propyloxy.

Lower alkoxycarbonyl-lower alkyl is, for example, C_1–C_4alkoxycarbonyl-C_1–C_4alkyl, such as methoxycarbonyl- or ethoxycarbonyl-methoxy, 2-methoxycarbonyl- or 2-ethoxycarbonyl-ethoxy, 3-methoxycarbonyl- or 3-ethoxycarbonyl-propyloxy or 4-ethoxycarbonylbutyloxy.

Lower alkoxy-lower alkenyl is, for example, C_1–C_4alkoxy-C_2–C_4alkenyl, such as 4-methoxybut-2-enyl.

Lower alkoxy-lower alkoxy is, for example, C_1–C_4alkoxy-C_2–C_4alkoxy, such as 2-methoxy-, 2-ethoxy- or 2-propyloxy-ethoxy, 3-methoxy- or 3-ethoxy-propyloxy or 4-methoxybutyloxy, especially 3-methoxypropyloxy or 4-methoxybutyloxy.

Lower alkoxy-lower alkoxy-lower alkyl is, for example, C_1–C_4alkoxy-C_1–C_4alkoxy-C $_1$–C_4alkyl, such as 2-methoxy-, 2-ethoxy- or 2-propyloxy-ethoxymethyl, 2-(2-methoxy-, 2-ethoxy- or 2-propyloxy-ethoxy)ethyl, 3-(3-methoxy- or 3-ethoxy-propyloxy)propyl or 4-(2-methoxybutyloxy)butyl, especially 2-(3-methoxypropyloxy)ethyl or 2-(4-methoxybutyloxy)ethyl.

Lower alkoxy-lower alkyl is, for example, C_1–C_4alkoxy-C_1–C_4alkyl, such as ethoxymethyl, propyloxymethyl, butyloxymethyl, 2-methoxy-, 2-ethoxy- or 2-propyloxy-ethyl, 3-methoxy- or 3-ethoxy-propyl or 4-methoxybutyl, especially 3-methoxypropyl or 4-methoxybutyl.

Lower alkoxypiperidino-lower alkyl is, for example, piperidino-, hydroxypiperidino- or lower alkoxypiperidino-C_1–C_4alkyl, such as piperidinomethyl, 4-hydroxypiperidinomethyl or 4-C_1–C_4alkoxy-, such as 4-methoxypiperidinomethyl.

Lower alkoxypiperidino-lower alkyl is, for example, C_1–C_4alkoxypiperidino-C_1–C_4alkyl, such as 4-C_1–C_4alkoxy-piperidinomethyl, especially 4-methoxypiperidinomethyl.

Lower alkyl may be straight-chained or branched and/or bridged and is, for example, corresponding C_1–C_7alkyl, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secondary butyl or tertiary butyl, or a pentyl, hexyl or heptyl group. Lower alkyl R_2 or R_3 is especially C_2–C_7alkyl, lower alkyl R_5 or R_7 is especially branched C_3–C_7alkyl and lower alkyl R_8 or R_3 is, for example, straight-chained, branched or bridged C_3–C_7alkyl.

Lower alkylamino is, for example, C_1–C_4alkylamino, such as methylamino, ethylamino, propylamino, butylamino, isobutylamino, secondary butylamino or tertiary butylamino.

Lower alkylamino-lower alkoxy is, for example, C_1–C_4alkylamino-C_1–C_4alkoxy, such as propylaminomethoxy, 2-methylamino-, 2-ethylamino-, 2-propylamino- or 2-butylamino-ethoxy, 3-ethylamino- or 3-propylamino-propyloxy or 4-methylaminobutoxy.

Lower alkylamino-lower alkyl is, for example, C_1–C_4alkylamino-C_1–C_4alkyl, such as propylaminomethyl, 2-methylamino-, 2-ethylamino-, 2-propylamino- or 2-butylamino-ethyl, 3-ethylamino- or 3-propylamino-propyl or 4-methylaminobutyl.

Lower alkylcarbamoyl-lower alkoxy is, for example, N-C_1–C_7alkylcarbamoyl-C $_1$–C_4alkoxy, such as methyl- or dimethyl-carbamoyl-C_1–C_4alkoxy, e.g. methylcarbamoylmethoxy, 2-methylcarbamoylethoxy or 3-methylcarbamoylpropyloxy.

Lower alkylenedioxy is, for example, methylenedioxy or ethylenedioxy, but can also be 1,3- or 1,2-propylenedioxy.

Lower alkylsulfamoyl-lower alkyl is, for example, N-C_1–C_7alkylsulfamoyl-C_1–C_4alkyl, such as N-methyl-, N-ethyl-, N-propyl- or N-butyl-sulfamoyl-C_1–C_4alkyl, such as N-methyl-, N-ethyl-, N-propyl- or N-butyl-sulfamoylmethyl, 2-(N-methylsulfamoyl)ethyl, 2-(N-butylsulfamoyl) ethyl, 3-(N-methylsulfamoyl)propyl, 3-(N-butylsulfamoyl) propyl, or 4-(N-methylsulfamoyl)butyl, 4-(N-butylsulfamoyl)butyl or 4-(N,N-dimethylsulfamoyl)butyl, especially N-methyl-, N-butyl- or N,N-dimethyl-sulfamoylmethyl.

Lower alkylthio-(hydroxy)-lower alkoxy is, for example, N-C_1–C_4alkylthio-C $_1$–C_4(hydroxy)alkoxy, such as 2-hydroxy-3-methylthiopropyloxy.

Oxazolyl-lower alkyl is, for example, oxazolyl-C_1–C_4alkyl, such as 2-(1,2,4-oxadiazol- 5-yl)ethyl, 3-(1,2,4-oxadiazol-5-yl)propyl or 4-(1,2,4-oxadiazol-5-yl)butyl.

Lower alkylthio-lower alkoxy is, for example, N-C_1–C_4alkylthio-C_1–C_4alkoxy, such as methylthio-C_1–C_4alkoxy, e.g. methylthiomethoxy, 2-methylthioethoxy or 3-methylthiopropyloxy.

Lower alkylthio-lower alkyl is, for example, N-C_1–C_4alkylthio-C_1–C_4alkyl, such as methylthio-C_1–C_4alkyl, e.g. methylthiomethyl, 2-methylthioethyl or 3-methylthiopropyl.

N'-Lower alkanoylpiperazino-lower alkoxy is, for example, N'-lower alkanoylpiperazino-C $_1$–C_4alkoxy, such as 4-acetylpiperazinomethoxy.

N'-Lower alkanoylpiperazino-lower alkyl is, for example, N'-C_2–C_7-lower alkanoylpiperazino-C $_1$–C_4alkyl, such as 4-acetylpiperazinomethyl.

N'-Lower alkylpiperazino-lower alkyl is, for example, N'-C_1–C_4alkylpiperazino-C $_1$–C_4alkyl, such as 4-methylpiperazinomethyl.

Oxo-lower alkoxy is, for example, oxo-C_1–C_4alkoxy, such as 3,3-dimethyl-2-oxo-butyloxy.

Piperazino-lower alkyl is, for example, piperazino-C_1–C_4alkyl, such as piperazinomethyl, 2-piperazinoethyl or 3-piperazinopropyl.

Piperidino-lower alkoxy is, for example, piperidino-C_1–C_4alkoxy, such as piperidinomethoxy, 2-piperidinoethoxy or 3-piperidinopropyloxy.

Piperidino-lower alkyl is, for example, piperidino-C_1–C_4alkyl, such as piperidinomethyl, 2-piperidinoethyl or 3-piperidinopropyl.

Polyhalo-lower alkanesulfonylamino-lower alkoxy is, for example, trifluoro-C_1–C_7alkanesulfonyl-C $_1$–C_4alkoxy, such as trifluoromethanesulfonylaminobutyloxy.

Polyhalo-lower alkanesulfonylamino-lower alkyl is, for example, trifluoro-C_1–C_7alkanesulfonyl-C_1–C_4alkyl, such as trifluoromethanesulfonylaminobutyl.

Pyrimidinyl-lower alkoxy is, for example, pyrimidinyl-C_1–C_4alkoxy, such as pyrimidinylmethoxy, 2-pyrimidinylethoxy or 3-pyrimidinylpropyloxy.

Pyrimidinyl-lower alkyl is, for example, pyrimidinyl-C_1–C_4alkyl, such as pyrimidinylmethyl, 2-pyrimidinylethyl or 3-pyrimidinylpropyl.

Pyrrolidino-lower alkoxy is, for example, pyrrolidino-C_2–C_4alkoxy, such as 2-pyrrolidinoethoxy or 3-pyrrolidinopropyloxy.

Pyrrolidino-lower alkyl is, for example, pyrrolidino-C_1–C_4alkyl, such as pyrrolidinomethyl, 2-pyrrolidinoethyl or 3-pyrrolidinopropyl.

S,S-Dioxothiomorpholino-lower alkyl is, for example, S,S-dioxothiomorpholino-C_1–C_4alkyl, such as S,S-dioxothiomorpholinomethyl or 2-(S,S-dioxo)thiomorpholinoethyl.

S-Oxothiomorpholino-lower alkyl is, for example, S-oxothiomorpholino-C_1–C_4alkyl, such as S-oxothiomorpholinomethyl or 2-(S-oxo)thiomorpholinoethyl.

Sulfamoyl-lower alkyl is, for example, sulfamoyl-C_1–C_4alkyl, such as sulfamoyl-C_1–C_4alkyl, such as sulfamoylmethyl, 2-sulfamoylethyl, 3-sulfamoylpropyl or 4-sulfamoylbutyl.

Tetrazolyl-lower alkyl is, for example, tetrazolyl-C_1–C_4alkyl, such as tetrazol-5-ylmethyl, 2-(tetrazol-5-yl) ethyl, 3-(tetrazol-5-yl)propyl or 4-(tetrazol-4-yl)butyl.

Thiazolinyl-lower alkoxy is, for example, thiazolinyl-C_1–C_4alkoxy, such as thiazolinylmethoxy, 2-thiazolinylmethoxy or 3-thiazolinylpropyloxy.

Thiazolinyl-lower alkyl is, for example, thiazolinyl-C_1–C_4alkyl, such as thiazolinylmethyl, 2-thiazolinylethyl or 3-thiazolinylpropyl.

Thiazolyl-lower alkoxy is, for example, thiazolyl-C_1–C_4alkoxy, such as thiazolylmethoxy, 2-thiazolylethoxy or 3-thiazolylpropyloxy.

Thiazolyl-lower alkyl is, for example, thiazolyl-C_1–C_4alkyl, such as thiazolylmethyl, 2-thiazolylethyl or 3-thiazolylpropyl.

Thiomorpholino-lower alkyl or S,S-dioxothiomorpholino-lower alkyl is, for example, thiomorpholino-C_1–C_4alkyl, such as -methyl or -ethyl, or S,S-dioxothiomorpholino-C_1–C_4alkyl, such as -methyl or -ethyl.

Depending on whether asymmetric carbon atoms are present, the compounds of the invention can be present as mixtures of isomers, especially as racemates, or in the form of pure isomers, especially optical antipodes.

Salts of compounds having salt-forming groups are especially acid addition salts, salts with bases or, where several salt-forming groups are present, can also be mixed salts or internal salts.

Salts are especially the pharmaceutically acceptable or non-toxic salts of compounds of formula I.

Such salts are formed, for example, by compounds of formula I having an acid group, for example a carboxy group or a sulfo group, and are, for example, salts thereof with suitable bases, such as non-toxic metal salts derived from metals of groups Ia, Ib, IIa and IIb of the Periodic Table of the Elements, for example alkali metal salts, especially lithium, sodium or potassium salts, or alkaline earth metal salts, for example magnesium or calcium salts, also zinc salts or ammonium salts, as well as salts formed with organic amines, such as unsubstituted or hydroxy-substituted mono-, di- or tri-alkylamines, especially mono-, di- or tri-lower alkylamines, or with quaternary ammonium bases, for example with methyl-, ethyl-, diethyl- or triethyl-amine, mono-, his- or tris-(2-hydroxy-lower alkyl)-amines, such as ethanol-, diethanol- or triethanol-amine, tris-(hydroxymethyl)-methylamine or 2-hydroxy-tert-butylamines, N,N-di-lower alkyl-N-(hydroxy-lower alkyl)-amines, such as N,N-dimethyl-N-(2-hydroxyethyl)-amine, or N-methyl-D-glucamine, or quaternary ammonium hydroxides, such as tetrabutylammonium hydroxide. The compounds of formula I having a basic group, for example an amino group, can form acid addition salts, for example with suitable inorganic acids, for example hydrohalic acids, such as hydrochloric acid or hydrobromic acid, or sulfuric acid with replacement of one or both protons, phosphoric acid with replacement of one or more protons, e.g. orthophosphoric acid or metaphosphoric acid, or pyrophosphoric acid with replacement of one or more protons, or with organic carboxylic, sulfonic, sulfo or phosphonic acids or N-substituted sulfamic acids, for example acetic acid, propionic acid, glycolic acid, succinic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, fumaric acid, malic acid, tartaric acid, gluconic acid, glucaric acid, glucuronic acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, salicylic acid, 4-aminosalicylic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, embonic acid, nicotinic acid or isonicotinic acid, as well as with amino acids, such as the α-amino acids mentioned hereinbefore, and with methanesulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 4-toluenesulfonic acid, naphthalene-2-sulfonic acid, 2- or 3-phosphoglycerate, glucose-6-phosphate, or N-cyclohexylsulfamic acid (forming cyclamates) or with other acidic organic compounds, such as ascorbic acid. Compounds of formula I having acid and basic groups can also form internal salts.

For isolation and purification purposes it is also possible to use pharmaceutically unacceptable salts.

The compounds of the present invention have enzyme-inhibiting properties. In particular, they inhibit the action of the natural enzyme renin. The latter passes from the kidneys into the blood where it effects the cleavage of angiotensinogen, releasing the decapeptide angiotensin I which is then cleaved in the lungs, the kidneys and other organs to form the octapeptide angiotensinogen II. The octapeptide increases blood pressure both directly by arterial vasoconstriction and indirectly by liberating from the adrenal glands the sodium-ion-retaining hormone aldosterone, accompanied by an increase in extracellular fluid volume. That increase can be attributed to the action of angiotensin II. Inhibitors of the enzymatic activity of renin bring about a reduction in the formation of angiotensin I. As a result a smaller amount of angiotensin II is produced. The reduced concentration of that active peptide hormone is the direct cause of the hypotensive effect of renin inhibitors.

The action of renin inhibitors is demonstrated inter alia experimentally by means of in vitro tests, the reduction in the formation of angiotensin I being measured in various systems (human plasma, purified human renin together with synthetic or natural renin substrate). Inter alia the following in vitro test is used: an extract of human renin from the kidney (0.5 mGU [milli-Goldblatt units]/ml) is incubated for one hour at 37° C. and pH 7.2 in 1-molar aqueous 2-N-(tris-hydroxymethylmethyl)amino-ethanesulfonic acid buffer solution with 23 μg/ml of synthetic renin substrate, the tetradecapeptide H-Asp-Arg-Val-Tyr-Ile-His-ProPhe-His-Leu-Leu-Val-Tyr-Ser-OH. The amount of angiotensin I formed is determined by radioimmunoassay. Each of the inhibitors according to the invention is added to the incubation mixture at different concentrations. The IC_{50} is

defined as the concentration of a particular inhibitor that reduces the formation of angiotensin I by 50%. In the in vitro systems the compounds of the present invention exhibit inhibiting activities at minimum concentrations of from approximately 10^{-6} to approximately 10^{-10} mol/l.

In animals deficient in salt, renin inhibitors bring about a reduction in blood pressure. Human renin differs from the renin of other species. In order to test inhibitors of human renin, primates (marmosets, Callithrix jacchus) are used, because human renin and primate renin are substantially homologous in the enzymatically active region. Inter alia the following in vivo test is used: the test compounds are tested on normotensive marmosets of both sexes having a body weight of approximately 350 g that are conscious, allowed to move freely and in their normal cages. The blood pressure and heart rate are measured via a catheter in the descending aorta and recorded radiometrically. The endogenous release of renin is stimulated by the combination of a 1-week low-salt diet and a single intramuscular injection of furosemide (5-(aminosulfonyl)-4-chloro- 2-[(2-furanylmethyl)amino]benzoic acid) (5 mg/kg). 16 hours after the injection of furosemide the test compounds are administered either directly into the femoral artery using an injection cannula or, in the form of a suspension or solution, via an oesophageal tube into the stomach, and their action on the blood pressure and heart rate are evaluated. In the in vivo test described, the compounds of the present invention have hypotensive action at doses of from approximately 0.003 to approximately 0.3 mg/kg i.v. and at doses of from approximately 0.31 to approximately 30 mg/kg p.o.

The compounds of the present invention also have the property of regulating, especially reducing, intra-ocular pressure.

The extent of the reduction in intra-ocular pressure after administration of a pharmaceutical active ingredient of formula (I) according to the present invention can be determined, for example, in animals, for example rabbits or monkeys. Two typical experimental procedures that illustrate the present invention, but are not intended to limit it in any way, are described hereinafter.

The in vivo test on a rabbit of the "Fauve de Bourgogne" type to determine the intraocular-pressure-reducing activity of topically applied compositions can be designed, for example, as follows. The intra-ocular pressure (IOP) is measured using an aplanation tonometer both before the experiment and at regular intervals of time. After a local anaesthetic has been administered, the suitably formulated test compound is applied topically in a precisely defined concentration (e.g. 0.000001–5% by weight) to one eye of the animal in question. The contralateral eye is treated, for example, with physiological saline. The measured values thus obtained are evaluated statistically.

The in vivo tests on monkeys of the species *Macaca Fascicularis* to determine the intraocular-pressure-reducing activity of topically applied compositions can be carried out, for example, as follows. The suitably formulated test compound is applied in a precisely defined concentration (e.g. 0.000001–5% by weight) to one eye of each monkey. The other eye of the monkey is treated correspondingly, for example with physiological saline. Before the start of the test the animals are anaesthetised with intramuscular injections of, for example, ketamine. At regular intervals of time, the intra-ocular pressure (IOP) is measured. The test is carried out and evaluated in accordance with the rules of "good laboratory practice" (GLP).

The compounds of the present invention can be used in the treatment of hypertension, congestive heart failure, cardiac hypertrophy, cardiac fibrosis, cardiomyopathy post-infarction, complications resulting from diabetes, such as nephropathy, vasculopathy and neuropathy, diseases of the coronary vessels, restenosis following angioplasty, raised intra-ocular pressure, glaucoma, abnormal vascular growth, hyperaldosteronism, anxiety states and cognitive disorders.

The groups of compounds mentioned below are not to be regarded as exclusive; rather, for example in order to replace general definitions with more specific definitions, parts of those groups of compounds can be interchanged or exchanged for the definitions given above, or omitted, as appropriate.

The invention relates especially to compounds of formula I wherein

R_1 is hydrogen, hydroxy, lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy, carboxy-lower alkoxy, lower alkoxycarbonyl-lower alkoxy, carbamoyl-lower alkoxy or N-mono- or N,N-di-lower alkylcarbamoyl-lower alkoxy,

R_2 is hydrogen, lower alkyl, cycloalkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, hydroxy, lower alkanoyloxy-lower alkyl, hydroxy-lower alkoxy, halo-(hydroxy)-lower alkoxy, lower alkanesulfonyl-(hydroxy)-lower alkoxy, amino-lower alkyl, lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl, lower alkanoylamino-lower alkyl, lower alkoxycarbonyl-amino-lower alkyl, amino-lower alkoxy, lower alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy, lower alkanoylamino-lower alkoxy, lower alkoxycarbonyl-amino-lower alkoxy, oxo-lower alkoxy, lower alkoxy, cycloalkoxy, lower alkenyloxy, cycloalkoxy-lower alkoxy, lower alkoxy-lower alkoxy, lower alkoxy-lower alkenyl, lower alkenyloxy-lower alkoxy, lower alkoxy-lower alkenyloxy, lower alkenyloxy-lower alkyl, lower alkanoyl-lower alkoxy, lower alkylthio-lower alkoxy, lower alkanesulfonyl-lower alkoxy, lower alkylthio-(hydroxy)-lower alkoxy, aryl-lower alkoxy, thiazolylthio-lower alkoxy or thiazolinylthio-lower alkoxy, imidazolylthio-lower alkoxy, optionally N-oxidised pyridylthio-lower alkoxy, pyrimidinylthio-lower alkoxy, cyano-lower alkoxy, lower alkoxycarbonyl-lower alkoxy, carbamoyl-lower alkoxy, N-mono- or N,N-di-lower alkylcarbamoyl-lower alkoxy, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, carbamoyl-lower alkyl or N-mono- or N,N-di-lower alkylcarbamoyl-lower alkyl,

R_3 is lower alkyl, polyhalo-lower alkyl, lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, hydroxy-lower alkyl, lower alkylthio-lower alkyl, lower alkanesulfonyl-lower alkyl, optionally partially hydrogenated or N-oxidised pyridyl-lower alkyl, thiazolyl-thio-lower alkyl or thiazolinylthio-lower alkyl, imidazolylthio-lower alkyl, optionally N-oxidised pyridylthio-lower alkyl, pyrimidinylthio-lower alkyl, amino-lower alkyl, lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl, lower alkanoyl-amino-lower alkyl, lower alkanesulfonylamino-lower alkyl, polyhalo-lower alkane-sulfonylamino-lower alkyl, pyrrolidino-lower alkyl, piperidino-lower alkyl, piperazino-, N'-lower alkylpiperazino- or N'-lower alkanoylpiperazino-lower alkyl, morpholino-lower alkyl, thiomorpholino-, S-oxothiomorpholino- or S,S-dioxothio-morpholino-lower alkyl, cyano-lower alkyl, carboxy-lower alkyl, lower alkoxy-carbonyl-lower alkyl, carbamoyl-lower alkyl, N-mono- or N,N-di-lower alkyl-carbamoyl-lower alkyl, cycloalkyl; phenyl or naphthyl that is

unsubstituted or mono-, di- or tri-substituted by lower alkyl, lower alkoxy, hydroxy, lower alkylamino, di-lower alkylamino, halogen and/or by trifluoromethyl; hydroxy, lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy, cycloalkoxy-lower alkoxy, hydroxy-lower alkoxy; phenyl-lower alkoxy or naphthyl-lower alkoxy that is unsubstituted or mono-, di- or tri-substituted by lower alkyl, lower alkoxy, hydroxy, lower alkylamino, di- lower alkylamino, halogen and/or by trifluoromethyl; lower alkoxy, polyhalo-lower alkoxy, lower alkylthio-lower alkoxy, lower alkanesulfonyl-lower alkoxy, optionally hydrogenated heteroaryl-lower alkoxy, optionally partially or fully hydrogenated heteroarylthio-lower alkoxy, such as thiazolylthio-lower alkoxy or thiazolinylthio-lower alkoxy, imidazolylthio-lower alkoxy, optionally N-oxidised pyridylthio-lower alkoxy, pyrimidinylthio-lower alkoxy, amino-lower alkoxy, lower alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy, lower alkanoylamino-lower alkoxy, lower alkanesulfonylamino-lower alkoxy, polyhalo-lower alkanesulfonylamino-lower alkoxy, pyrrolidino-lower alkoxy, piperidino-lower alkoxy, piperazino-, N'-lower alkylpiperazino- or N'-lower alkanoylpiperazino-lower alkoxy, morpholino-lower alkoxy, thiomorpholino-, S-oxothiomorpholino- or S,S-dioxothiomorpholino-lower alkoxy, cyano-lower alkoxy, carboxy-lower alkoxy, lower alkoxycarbonyl-lower alkoxy, carbamoyl-lower alkoxy or N-mono- or N,N-di-lower alkylcarbamoyl-lower alkoxy or together with R_4 is lower alkylenedioxy or a fused-on benzo or cyclohexeno ring,

R_4 together with R_3 is lower alkylenedioxy or a fused-on benzo or cyclohexeno ring, or is hydrogen, lower alkyl, hydroxy, lower alkoxy or cycloalkoxy,

X is methylene or hydroxymethylene,

R_5 is lower alkyl or cycloalkyl,

R_6 is amino, lower alkylamino, di-lower alkylamino or lower alkanoylamino,

R_7 is lower alkyl, lower alkenyl, cycloalkyl, or phenyl- or naphthyl-lower alkyl that is unsubstituted or mono-, di- or tri-substituted by lower alkyl, lower alkoxy, hydroxy, lower alkylamino, di-lower alkylamino, halogen and/or by trifluoromethyl, and

R_8 is lower alkyl, cycloalkyl, hydroxy-lower alkyl, lower alkanoyloxy-lower alkyl, lower alkoxy-lower alkyl or lower alkenyloxy-lower alkyl, amino-lower alkyl, lower alkanoylamino-lower alkyl, N-mono- or N,N-di-lower alkylamino-lower alkyl, optionally hydroxylated or lower alkoxylated piperidino-lower alkyl, such as piperidino-lower alkyl, hydroxypiperidino-lower alkyl or lower alkoxypiperidino-lower alkyl, piperazino-, N'-lower alkylpiperazino- or N'-lower alkanoylpiperazino-lower alkyl, unsubstituted or lower alkylated morpholino-lower alkyl, such as morpholino-lower alkyl or dimethylmorpholino-lower alkyl, or optionally S-oxidised thiomorpholino-lower alkyl, such as thiomorpholino-lower alkyl, S,S-dioxothiomorpholino-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, carbamoyl-lower alkyl, N-mono- or N,N-di-lower alkylcarbamoyl-lower alkyl, dicarboxy-lower alkyl, di-lower alkoxycarbonyl-lower alkyl, dicarbamoyl-lower alkyl, di-(N-mono- or N,N-di-lower alkylcarbamoyl)-lower alkyl, carboxy-(hydroxy)-lower alkyl, lower alkoxy-carbonyl-(hydroxy)-lower alkyl or carbamoyl-(hydroxy)-lower alkyl, cyano-lower alkyl, lower alkanesulfonyl-lower alkyl, sulfamoyl-lower alkyl, lower alkyl-sulfamoyl-lower alkyl, di-lower alkylsulfamoyl-lower alkyl, thiocarbamoyl-lower alkyl, lower alkylthiocarbamoyl-lower alkyl, di-lower alkylthiocarbamoyl-lower alkyl, pyrrolidinyl, imidazolyl, benzimidazolyl, oxadiazolyl, pyridyl, oxopiperidinyl, quinolinyl, unsubstituted or N-lower alkanoylated piperidyl or pyrrolidinyl, imidazolyl-lower alkyl, benzimidazolyl-lower alkyl, oxadiazolyl-lower alkyl, pyridyl-lower alkyl, unsubstituted or N-lower alkanoylated piperidyl-lower alkyl or pyrrolidinyl-lower alkyl, oxopiperidinyl-lower alkyl, quinolinyl-lower alkyl, morpholino-carbonyl-lower alkyl or unsubstituted or N-lower alkanoylated piperidyl-lower alkyl,

and the salts thereof.

The invention relates especially to compounds of formula I wherein

R_1 is hydrogen,

R_2 is lower alkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkoxy, lower alkoxy-lower alkoxy-lower alkyl; phenyl-lower alkoxy that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen, nitro and/or by amino; optionally N-oxidised pyridyl-lower alkoxy, lower alkylthio-lower alkoxy, lower alkane-sulfonyl-lower alkoxy, lower alkanoyl-lower alkoxy, optionally N-oxidised pyridyl-lower alkoxy, cyano-lower alkoxy, carboxy-lower alkoxy, lower alkoxycarbonyl-lower alkoxy, carbamoyl-lower alkoxy, lower alkylcarbamoyl-lower alkoxy or di-lower alkylcarbamoyl-lower alkoxy,

R_3 is hydrogen, lower alkyl, hydroxy, lower alkoxy or polyhalo-lower alkoxy or together with R_4 is lower alkylenedioxy,

R_4 is hydrogen or together with R_3 is lower alkylidenedioxy,

X is methylene or hydroxymethylene,

R_5 is lower alkyl or cycloalkyl,

R_6 is amino, lower alkylamino, di-lower alkylamino or lower alkanoylamino,

R_7 is lower alkyl, and

R_8 is lower alkyl, hydroxy,lower alkyl, lower alkanoyl-lower alkyl, lower alkoxy-lower alkyl, lower alkenyloxy-lower alkyl, amino-lower alkyl, lower alkanoylamino-lower alkyl, such as 2-(C_1–C_4alkanoylamino)-2-methyl-propyl, such as 2-acetylamino-2-methyl-propyl or 2-formylamino-2-methyl-propyl, N-mono- or N,N-di-lower alkylamino-lower alkyl, piperidino-lower alkyl, hydroxypiperidino-lower alkyl, lower alkoxypiperidino-lower alkyl, morpholino-lower alkyl, dimethylmorpholino-lower alkyl, thiomorpholino-lower alkyl, S,S-dioxothiomorpholino-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, carbamoyl-lower alkyl, N-mono- or N,N-di-lower alkylcarbamoyl-lower alkyl, carboxy-(hydroxy)-lower alkyl, lower alkoxycarbonyl-(hydroxy)-lower alkyl, carbamoyl-(hydroxy)-lower alkyl, 5- or 6-membered carboxycycloalkyl-lower alkyl, 5- or 6-membered lower alkoxycarbonyl-cycloalkyl-lower alkyl, 5- or 6-membered carbamoylcycloalkyl-lower alkyl, 5- or 6-membered N-mono- or N,N-di-lower alkylcarbamoylcycloalkyl-lower alkyl, cyano-lower alkyl, lower alkanesulfonyl-lower alkyl, sulfamoyl-lower alkyl, lower alkylsulfamoyl-lower alkyl, or di-lower alkylsulfamoyl-lower alkyl, imidazolyl-lower alkyl, oxopyrrolidinyl-lower alkyl, benzimidazolyl-lower alkyl, oxadiazolyl-lower alkyl, pyridyl-lower alkyl,

oxopiperidinyl-lower alkyl or quinolinyl-lower alkyl, piperidin-4-yl-lower alkyl or 1-C_1–C_7-lower alkanoylpiperidin-4-yl-lower alkyl,

and the salts thereof.

The invention relates above all to compounds of formula I wherein

R_1 and R_4 are hydrogen,

R_2 is C_1–C_4alkoxy-C_1–C_4alkoxy, such as 3-methoxypropyloxy, or C_1–C_4alkoxy-C_1–C_4alkyl, such as 4-methoxybutyl,

R_3 is C_1–C_4alkyl, such as isopropyl or tert-butyl, or C_1–C_4alkoxy, such as methoxy,

R_6 is amino,

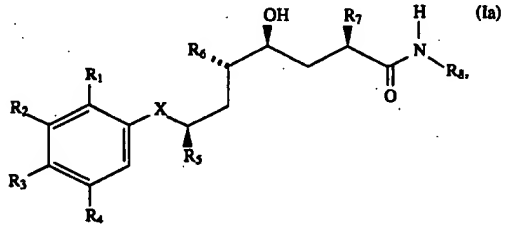
X is methylene,

R_5 and R_7 are branched C_1–C_4alkyl, such as isopropyl, and

R_8 is carbamoyl-C_1–C_4alkyl, such as 2- or 3-carbamoylpropyl, 2-(3-carbamoyl)propyl or 1-(2-carbamoyl-2-methyl)propyl, N-C_1–C_4alkylcarbamoyl-C_1–C_4alkyl, such as 3-(N-methylcarbamoyl)propyl, 1-(N-methylcarbamoyl)prop-2-yl, 2-(N-methyl-carbamoyl)prop-1-yl, especially 2(R)-(N-methylcarbamoyl)prop-1-yl, N,N-di-C_1–C_4alkylcarbamoyl-C_1–C_4alkyl, such as N,N-dimethylcarbamoylmethyl or 2-(N,N-dimethylcarbamoyl)ethyl, 3-(N,N-dimethylcarbamoyl)propyl, morpholino-C_1–C_4alkyl, such as 2-morpholinoethyl, 3-morpholinopropyl or 1-(2-morpholino- 2-methyl-)propyl, thiomorpholino-C_1–C_4alkyl, such as 2-thiomorpholinoethyl, 4-(1-C_1–C_4alkanoylpiperidyl)-C_1–C_4alkyl, such as 2-[4-(1-acetyl)piperidinyl]ethyl, 2-oxopyrrolidinyl-C_1–C_4alkyl, such as 2-oxopyrrolidin-5(S)-ylmethyl or 2-oxopyrrolidin- 5(R)-ylmethyl,

and the salts thereof.

Especially effective are those compounds of formula I wherein at least one, for example one, two, or preferably all four, of the asymmetric carbon atoms of the main chain have the stereochemical configuration shown in formula Ia



(Ia)

the variables each being as defined above, and the pharmaceutically acceptable salts thereof.

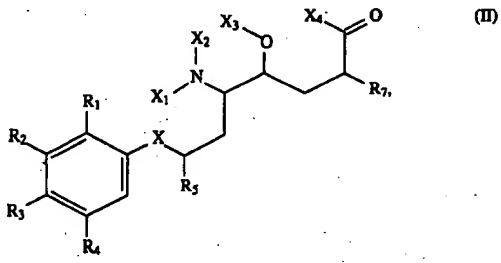
Accordingly, the invention relates preferably to compounds of formula I wherein at least one, for example one, two, or preferably all four, of the asymmetric carbon atoms of the main chain have the stereochemical configuration shown in formula Ia.

The invention relates very especially to those of the above-defined compounds of formulae I and Ia that are described as being preferred wherein X is methylene.

The invention relates specifically to the compounds of formula I mentioned in the Examples and to the salts thereof, especially the pharmaceutically acceptable salts thereof.

The process according to the invention for the preparation of compounds of formula I comprises

a) reacting a compound of formula II



(II)

wherein

X_1 is lower alkyl, lower alkanoyl or an amino-protecting group,

X_2 is hydrogen or together with X_3 is a bivalent protecting group,

X_3 is hydrogen or a hydroxy-protecting group or together with X_2 is a bivalent protecting group or together with X_4 is a direct bond,

X_4 is free or reactively etherified or esterified hydroxy or together with X_3 is a direct bond, and

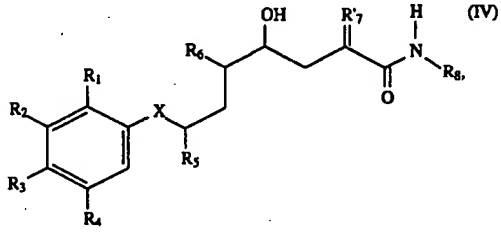
R_1, R_2, R_3, R_4, X, R_5, R_6 and R_7 are as defined for formula I, with an amine of formula III

$$H_2N—R_8 \quad \text{(III)},$$

wherein

R_8 has one of the meanings given for formula I, with the formation of an amide bond, and removing any protecting groups present, or

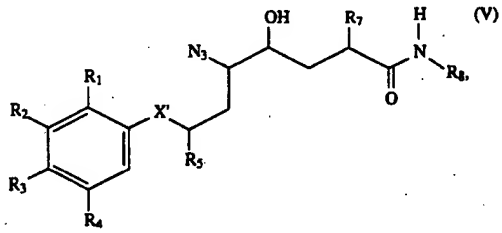
b) in a carboxylic acid amide of formula IV



(IV)

wherein R_1, R_2, R_3, R_4, X, R_5, R_6, R_7 and R_8 are as defined for formula I and R'_7 is a lower alkylidene or aryl-lower alkylidene group corresponding to the lower alkyl or aryl-lower alkyl group R_7, free functional groups being present, if desired, in protected form, or in a salt thereof, reducing the group R'_7 to R_7 by treatment with a hydrogenating agent, or

c) for the preparation of compounds of formula I wherein R_6 is amino, in a 5-azidocarboxylic acid derivative of formula V



(V)

wherein

R_1, R_2, R_3, R_4, R_5, R_7 and R_8 are as defined for formula I, X' is methylene or free or esterified or etherified hydroxymethyl, and free functional groups are present, if desired, in protected form, or in a salt thereof,

reducing the azido group to amino, if desired with the freeing of hydroxymethyl X or the reduction of X' to methylene X, and removing any protecting groups present, and, if desired, converting a compound of formula I having at least one salt-forming group obtainable by one of the above-mentioned processes a) to c) into its salt, or converting an obtainable salt into the free compound or into a different salt and/or separating mixtures of isomers that may be obtainable and/or convening a compound of formula I according to the invention into a different compound of formula I according to the invention.

Functional groups in starting materials the reaction of which is to be avoided, especially carboxy, amino, hydroxy and mercapto groups, can be protected by suitable protecting groups (conventional protecting groups) which are customarily used in the synthesis of peptide compounds, and also in the synthesis of cephalosporins and penicillins as well as nucleic acid derivatives and sugars. Those protecting groups may already be present in the precursors and are intended to protect the functional groups in question against undesired secondary reactions, such as acylation, etherification, esterification, oxidation, solvolysis, etc.. In certain cases the protecting groups can additionally cause the reactions to proceed selectively, for example stereoselectively. It is characteristic of protecting groups that they can be removed easily, i.e. without undesired secondary reactions taking place, for example by solvolysis, reduction, photolysis, and also enzymatically, for example under physiological conditions. Protecting groups may also be present in the end products, however. Compounds of formula I having protected functional groups may have greater metabolic stability or pharmacodynamic properties that are better in some other way than the corresponding compounds having free functional groups.

The protection of functional groups by such protecting groups, the protecting groups themselves and the reactions for their removal are described, for example, in standard works such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in Th. W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York 1981, in "The Peptides", Volume 3 (E. Gross and J. Meienhofer, eds.), Academic Press, London and New York 1981, in "Methoden der organischen Chemie", Houben-Weyl, 4th edition, Volume 15/I, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jescheit, "Aminosäuren, Peptide, Proteine" ("Amino acids, peptides, proteins"), Verlag Chemie, Weinheim, Deerfield Beach and Basle 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" ("The Chemistry of Carbohydrates: monosaccharides and derivatives"), Georg Thieme Verlag, Stuttgart 1974.

Process variant a) (Formation of the amide bond):

Amino-protecting groups X_1 are, for example, acyl groups other than lower alkanoyl, also arylmethyl, lower alkylthio, 2-acyl-lower alk-1-enyl or silyl. The group X_1-N(X_2)- can also be in the form of an azido group.

Acyl groups other than lower alkanoyl are, for example, halo-lower alkanoyl, for example 2-haloacetyl, such as 2-chloro-, 2-bromo-, 2-iodo-, 2,2,2-trifluoro- or 2,2,2-trichloro-acetyl, unsubstituted or substituted, for example halo-, lower alkoxy- or nitro-substituted, benzoyl, for example benzoyl, 4-chlorobenzoyl, 4-methoxybenzoyl or 4-nitrobenzoyl, or lower alkoxycarbonyl that is branched in the 1-position of the lower alkyl radical or suitably substituted in the 1- or 2-position, for example tertiary lower alkoxycarbonyl, such as tert-butoxycarbonyl, arylmethoxycarbonyl having one or two aryl radicals which are phenyl that is unsubstituted or mono- or poly-substituted, for example, by lower alkyl, for example tertiary lower alkyl, such as tertiary butyl, lower alkoxy, such as methoxy, hydroxy, halogen, such as chlorine, and/or by nitro, for example benzyloxycarbonyl, unsubstituted or substituted benzyloxycarbonyl, such as 4-nitrobenzyloxycarbonyl, diphenylmethoxycarbonyl, fluorenylmethoxycarbonyl or substituted diphenylmethoxycarbonyl, such as di(4-methoxyphenyl)methoxycarbonyl, aroylmethoxycarbonyl wherein the aroyl group is preferably benzoyl that is unsubstituted or substituted, for example, by halogen, such as bromine, for example phenacyloxycarbonyl, 2-halo-lower alkoxycarbonyl, for example 2,2,2-trichloroethoxycarbonyl, 2-bromoethoxycarbonyl or 2-iodo-ethoxycarbonyl, 2-(tri-substituted silyl)-lower alkoxycarbonyl, for example 2-tri-lower alkylsilyl-lower alkoxycarbonyl, for example 2-trimethylsilylethoxycarbonyl or 2-(di-n-butyl-methyl-silyl)-ethoxycarbonyl, or triarylsilyl-lower alkoxycarbonyl, for example 2-triphenylsilylethoxycarbonyl.

In a 2-acyl-lower alk-1-enyl radical that can be used as an amino-protecting group, acyl is, for example, the corresponding radical of a lower alkanecarboxylic acid, of a benzoic acid that is unsubstituted or substituted, for example, by lower alkyl, such as methyl or tertiary butyl, lower alkoxy, such as methoxy, halogen, such as chlorine, and/or by nitro, or especially of a carbonic acid semiester, such as a carbonic acid lower alkyl semiester. Corresponding protecting groups are especially 1-lower alkanoyl-prop-1-en-2-yl, for example 1-acetyl-prop-1-en-2-yl, or lower alkoxycarbonyl-prop-1-en-2-yl, for example 1-ethoxy-carbonyl-prop- 1-en-2-yl.

A silylamino group is, for example, a tri-lower alkylsilylamino group, for example trimethylsilylamino. The silicon atom of the silylamino group can also be substituted by only two lower alkyl groups, for example methyl groups, and by the amino group or carboxy group of a second molecule of formula I. Compounds having such protecting groups can be prepared, for example, using dimethylchlorosilane as silylating agent.

An amino group can also be protected by conversion into the protonated form; suitable corresponding anions are especially those of strong inorganic acids, such as sulfuric acid, phosphoric acid or hydrohalic acids, for example the chlorine or bromine anion, or of organic sulfonic acids, such as p-toluenesulfonic acid.

Preferred amino-protecting groups X_1 are acyl radicals of carbonic acid semiesters, such as lower alkoxycarbonyl, especially tert-butyloxycarbonyl or fluorenylmethoxycarbonyl, unsubstituted or lower alkyl-, lower alkoxy-, nitro- and/or halo-substituted α-phenyl- or α,α-diphenyl-lower alkoxycarbonyl, such as benzyloxycarbonyl, p-nitrobenzyloxy-carbonyl or diphenylmethoxycarbonyl, or 2-halo-lower alkoxycarbonyl, e.g. 2,2,2-trichloroethoxycarbonyl, also trityl or formyl.

Hydroxy-protecting groups X_3 are, for example, acyl groups, for example lower alkanoyl that is substituted by halogen, such as chlorine, for example 2,2-dichloroacetyl, or especially acyl radicals of a carbonic acid semiester mentioned for protected amino groups. A preferred hydroxy-protecting group is, for example, 2,2,2-trichloroethoxycarbonyl, 4-nitrobenzyloxycarbonyl, diphenylmethoxycarbonyl or trityl. A further suitable hydroxy-protecting group X_3 is tri-lower alkylsilyl, for example trimethylsilyl, triisopropylsilyl or dimethyl-tert-butylsilyl, a readily removable etherifying group, for example an alkyl group, such as tertiary lower alkyl, for

example tertiary butyl, an oxa- or a thia-aliphatic or -cycloaliphatic, especially 2-oxa- or 2-thia-aliphatic or -cycloaliphatic, hydrocarbon radical, for example 1-lower alkoxy-lower alkyl or 1-lower alkylthio-lower alkyl, for example methoxymethyl, 1-methoxyethyl, 1-ethoxyethyl, methylthiomethyl, 1-methylthioethyl or 1-ethylthioethyl, or 2-oxa- or 2-thia-cycloalkyl having from 5 to 7 ring atoms, for example 2-tetrahydrofuryl or 2-tetrahydropyranyl, or a corresponding thia analogue, and also 1-phenyl-lower alkyl, for example benzyl, diphenylmethyl or trityl, wherein the phenyl radicals can be substituted, for example, by halogen, for example chlorine, lower alkoxy, for example methoxy, and/or by nitro.

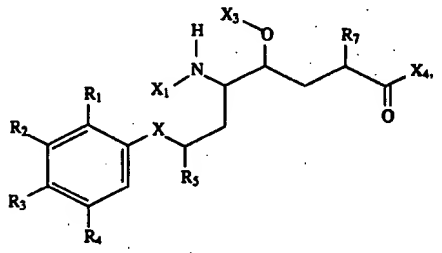
Bivalent protecting groups formed by X_2 and X_3 together are, for example, methylene groups substituted by one or two alkyl radicals and are accordingly unsubstituted or substituted alkylidene, such as lower alkylidene, for example isopropylidene, cycloalkylidene, such as cyclohexylidene, also carbonyl or benzylidene.

If X_4 is reactively etherified or esterified hydroxy, the terminal group —(=O)—X_4 is a reactively functionally modified carboxylic acid function and is, for example, in the form of an activated ester or anhydride. The reactive acid derivatives can also be formed in situ.

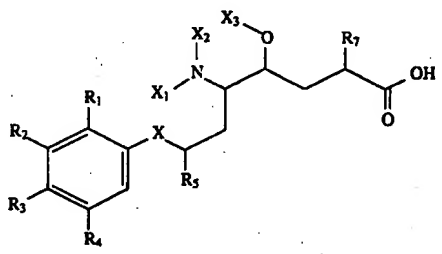
Such activated esters of compounds of formula II are especially esters unsaturated at the linking carbon atom of the esterifying radical, for example of the vinyl ester type, such as vinyl esters (obtainable, for example, by transesterification of a corresponding ester with vinyl acetate; activated vinyl ester method), carbamoyl esters (obtainable, for example, by treatment of the corresponding acid with an isoxazolium reagent; 1,2-oxazolium or Woodward method), or 1-lower alkoxyvinyl esters (obtainable, for example, by treatment of the corresponding acid with a lower alkoxyacetylene; ethoxyacetylene method), or esters of the amidino type, such as N,N'-disubstituted amidino esters (obtainable, for example, by treatment of the corresponding acid with a suitable N,N'-disubstituted carbodiimide, for example N,N'-dicyclohexylcarbodiimide; carbodiimide method), or N,N-disubstituted amidino esters (obtainable, for example, by treatment of the corresponding acid with an N,N-disubstituted cyanamide; cyanamide method), suitable aryl esters, especially phenyl esters suitably substituted by electron-attracting substituents (obtainable, for example, by treatment of the corresponding acid with a suitably substituted phenol, for example 4-nitrophenol, 4-methylsulfonylphenol, 2,4,5-trichlorophenol, 2,3,4,5,6-pentachlorophenol or 4-phenyldiazophenol, in the presence of a condensation agent, such as N,N'-dicyclohexylcarbodiimide; activated aryl esters method), cyanomethyl esters (obtainable, for example, by treatment of the corresponding acid with chloroacetonitrile in the presence of a base; cyanomethyl esters method), thioesters, especially unsubstituted or substituted, for example nitro-substituted, phenylthio esters (obtainable, for example, by treatment of the corresponding acid with unsubstituted or substituted, for example nitro-substituted, thiophenols, inter alia by the anhydride or carbodiimide method; activated thiol esters method), or especially amino or amido esters (obtainable, for example, by treatment of the corresponding acid with an N-hydroxyamino or N-hydroxyamido compound, for example N-hydroxysuccinimide, N-hydroxypiperidine, N-hydroxyphthalimide, N-hydroxy-5-norbornene-2,3-dicarboxylic acid imide, 1-hydroxybenzotriazole or 3-hydroxy-3,4-dihydro-1,2,3-benzotriazin-4-one, for example by the anhydride or carbodiimide method; activated N-hydroxy esters method). Internal esters, for example γ-lactones, can also be used.

Anhydrides of acids of formula II may be symmetric or preferably mixed anhydrides of those acids, for example anhydrides with inorganic acids, such as acid halides, especially acid chlorides (obtainable, for example, by treatment of the corresponding acid with thionyl chloride, phosphorus pentachloride or oxalyl chloride; acid chloride method), azides (obtainable, for example, from a corresponding acid ester via the corresponding hydrazide and treatment thereof with nitrous acid; azide method), anhydrides with carbonic acid semiesters, for example carbonic acid lower alkyl semiesters (obtainable, for example, by treatment of the corresponding acid with chloroformic acid lower alkyl esters or with a 1-lower alkoxycarbonyl-2-lower alkoxy-1,2-dihydroquinoline; mixed O-alkyl-carbonic acid anhydrides method), or anhydrides with dihalogenated, especially dichlorinated, phosphoric acid (obtainable, for example, by treatment of the corresponding acid with phosphorus oxychloride; phosphorus oxychloride method), anhydrides with other phosphoric acid derivatives (for example those obtainable with phenyl-N-phenylphosphoramidochloridate) or with phosphorous acid derivatives, or anhydrides with organic acids, such as mixed anhydrides with organic carboxylic acids (obtainable, for example, by treatment of the corresponding acid with an unsubstituted or substituted lower alkane- or phenyl-lower alkane-carboxylic acid halide, for example phenylacetic acid chloride, pivalic acid chloride or trifluoroacetic acid chloride; mixed carboxylic acid anhydrides method) or with organic sulfonic acids (obtainable, for example, by treatment of a salt, such as an alkali metal salt, of the corresponding acid with a suitable organic sulfonic acid halide, such as a lower alkane- or aryl-, for example methane- or p-toluene-sulfonic acid chloride; mixed sulfonic acid anhydrides method) and symmetric anhydrides (obtainable, for example, by condensation of the corresponding acid in the presence of a carbodiimide or 1-diethylaminopropyne; symmetric anhydrides method).

Preferred starting materials of formula II are compounds of formulae IIa, IIb and IIc



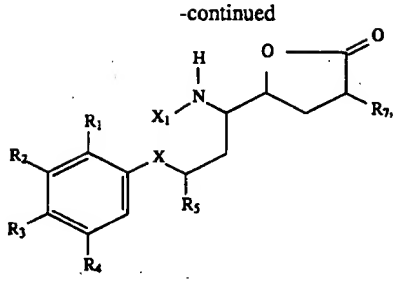
(IIa)



(IIb)

and

-continued



(IIc)

wherein

X_1 is an amino-protecting group, especially tert-butyloxycarbonyl,

X_2 together with X_3 is a bivalent protecting group, especially lower alkylidene, such as isopropylidene, and

X_3 in formula IIa is hydrogen or tri-lower alkylsilyl, especially tert-butyl(dimethyl)silyl, or in formula IIb, together with X_2, is a bivalent protecting group, especially lower alkylidene, such as isopropylidene, and

X_4 is hydroxy, lower alkoxy or halogen, such as chlorine.

As mentioned, derivatives of carboxylic acids that are used as acylating agents may also be formed in situ. For example, N,N'-disubstituted amidino esters may be formed in situ by reacting a mixture of the acid used as acylating agent and the starting material of formula III in the presence of a suitable N,N'-disubstituted carbodiimide, for example N,N'-cyclohexylcarbodiimide. In addition, amino or amido esters of the acids used as acylating agents may be formed in the presence of the starting material of formula III to be acylated, by reacting a mixture of the corresponding acid and amino starting materials in the presence of an N,N'-disubstituted carbodiimide, for example N,N'-dicyclohexylcarbodiimide, and of an N-hydroxyamine or N-hydroxyamide, for example N-hydroxysuccinimide, where appropriate in the presence of a suitable base, for example 4-dimethylamino-pyridine.

The condensation to form an amide bond can be carried out in a manner known per se, for example as described in standard works, such as Houben-Weyl, "Methoden der organischen Chemie", 4th edition, Volume 15/II (1974), Volume IX (1955), Volume E 11 (1985), Georg Thieme Verlag, Stuttgart, "The Peptides" (E. Gross and J. Meienhofer, eds.), Volumes 1 and 2, Academic Press, London and New York, 1979/1980, or M. Bodansky, "Principles of Peptide Synthesis", Springer-Verlag, Berlin 1984.

The condensation of a free carboxylic acid with the corresponding amine can be carried out preferably in the presence of one of the customary condensation agents. Customary condensation agents are, for example, carbodiimides, for example diethyl-, dipropyl-, N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide or especially dicyclohexylcarbodiimide, also suitable carbonyl compounds, for example carbonyldiimidazole, 1,2-oxazolium compounds, for example 2-ethyl-5-phenyl-1,2-oxazolium-3'-sulfonate and 2-tert-butyl-5-methylisoxazolium perchlorate, or a suitable acylamino compound, for example 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, also activated phosphoric acid derivatives, for example diphenylphosphoryl azide, diethylphosphoryl cyanide, phenyl-N-phenylphosphoromidochloridate, bis(2-oxo-3-oxazolidinyl)phosphinic acid chloride or 1-benzotriazolyloxy-tris(dimethylamino)phosphonium hexafluorophosphate.

If desired, an organic base may be added, for example a tri-lower alkylamine having bulky radicals, for example ethyldiisopropylamine, and/or a heterocyclic base, for example pyridine, N-methylmorpholine or preferably 4-dimethylaminopyridine.

The condensation of activated esters, reactive anhydrides or reactive cyclic amides with the corresponding amines is customarily carried out in the presence of an organic base, for example simple tri-lower alkylamines, for example triethylamine or tributylamine, or one of the above-mentioned organic bases. If desired, a condensation agent may additionally be used, for example as described for free carboxylic acids.

The condensation of acid anhydrides with amines can be effected, for example, in the presence of inorganic carbonates, for example ammonium or alkali metal carbonates or hydrogen carbonates, such as sodium or potassium carbonate or hydrogen carbonate (usually together with a sulfate).

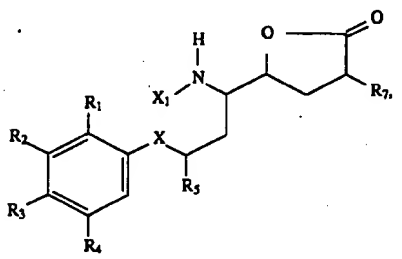
Carboxylic acid chlorides, for example the chlorocarbonic acid derivatives derived from the acid of formula II, are condensed with the corresponding amines preferably in the presence of an organic amine, for example the above-mentioned tri-lower alkylamines or heterocyclic bases, where appropriate in the presence of a hydrogen sulfate.

The condensation is preferably carried out in an inert, aprotic, preferably anhydrous, solvent or solvent mixture, for example in a carboxylic acid amide, for example formamide or dimethylformamide, a halogenated hydrocarbon, for example methylene chloride, carbon tetrachloride or chlorobenzene, a ketone, for example acetone, a cyclic ether, for example tetrahydrofuran, an ester, for example ethyl acetate, or a nitrile, for example acetonitrile, or in a mixture thereof, as appropriate at reduced or elevated temperature, for example in a temperature range of from approximately −40° C. to approximately +100° C., preferably from approximately −10° C. to approximately +50° C., and in the case where arylsulfonyl esters are used also at approximately from +100° C. to +200° C., and without an inert gas or under an inert gas atmosphere, for example a nitrogen or argon atmosphere.

Aqueous, for example alcoholic, solvents, for example ethanol, or aromatic solvents, for example benzene or toluene, may also be used. When alkali metal hydroxides are present as bases, acetone can also be added where appropriate.

The condensation can also be carded out in accordance with the technique known as solid-phase synthesis which originates from R. Merrifield and is described, for example, in Angew. Chem. 97, 801–812 (1985), Naturwissenschaften 71, 252–258 (1984) or in R. A. Houghten, Proc. Natl. Acad. Sci. U.S.A. 82, 5131–5135 (1985).

A preferred variant of that process is carried out by reacting, as the activated ester, an internal ester (γ-lactone) derived from the carboxylic acid of formula I and having the formula IIc



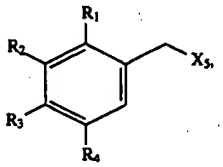
(IIc)

wherein X is methylene, with the compound of formula III, free functional groups present in the reactants, with the exception of the groups participating in the reaction, being if desired, as stated above, in protected form and any protecting groups being removed as described above. The

opening of the lactone ring with the formation of the amide bond is carried out under the conditions described above, optionally in the presence of a suitable catalyst. In particular, a γ-lactone IIc may be reacted with a primary amine III without a solvent or in the presence of a polar solvent, for example a lower alcohol, such as methanol or ethanol, a polar ether, such as tetrahydrofuran or dioxane, a nitrile, such as acetonitrile, an amide, such as dimethylformamide, N,N-dimethylacetamide, N-methyl-pyrrolidone or hexamethylphosphoric acid triamide, a urea, for example N,N'-dimethyl-N,N'-propylenylurea, a lower alkoxy-lower alkanol, for example diethylene glycol mono-methyl ether, in dimethyl sulfoxide or in a mixture of the mentioned solvents or in a mixture of one or more of the mentioned solvents with water, at temperatures of from room temperature to 150° C., preferably approximately from 20° C. to 100° C., and in the presence of a catalyst, such as 2-hydroxypyridine and/or triethylamine, the comments made above applying in respect of the protecting groups.

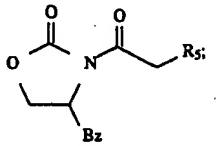
In another preferred variant of that process the starting material used is a compound of formula IIb wherein X is methylene, which is reacted with the reactant of formula III in the presence of a cyanophosphonic acid diester, for example cyanophosphonic acid diethyl ester, and a tertiary organic amine, such as a tri-lower alkylamine, for example trimethyl-amine, and in a polar solvent, for example a nitrile, such as acetonitrile, an amide, such as dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone or hexamethyl-phosphoric acid triamide, a urea, for example N,N'-dimethyl-N,N'-propylenylurea, a lower alkoxy-lower alkanol, for example diethylene glycol monomethyl ether, in dimethyl sulfoxide or in a mixture of the mentioned solvents or in a mixture of one or more of the mentioned solvents with water, at temperatures of from −30° C. to 100° C., preferably from 20° C. to 80° C., the comments made above applying in respect of the protecting groups.

Starting materials of formula II can be prepared, for example, by reacting a compound of formula VI



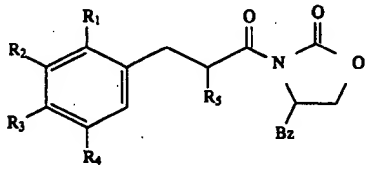
(VI)

wherein X_5 is free or reactively esterified hydroxy, especially halogen, such as bromine, with a compound of formula VII



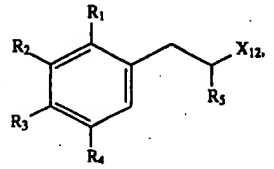
(VII)

in the resulting compound of formula VIII



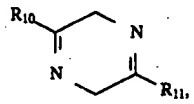
(VIII)

hydrolysing the 4-benzyl-2-oxo-oxazolidin-1-ylcarbonyl group selectively to carboxy, for example by means of lithium hydroxide/hydrogen peroxide; reducing the carboxy group to hydroxymethyl, for example by means of sodium borohydride/iodine in tetrahydrofuran; halogenating the hydroxymethyl group, for example with N-bromosuccinimide/triphenyl-phosphine in dichloromethane, and reacting the reaction product of formula IX



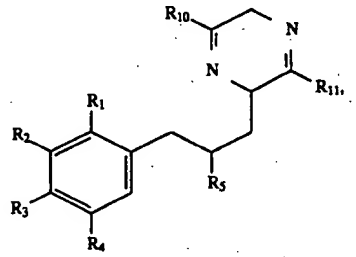
(IX)

wherein X_{12} is halomethyl, with a compound of formula X



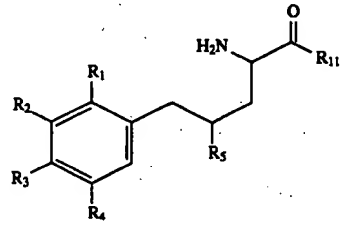
(X)

wherein R_{10} and R_{11} are identical or different lower alkoxy groups; hydrolysing the resulting compound of formula XI



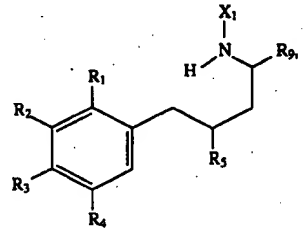
(XI)

wherein R_1, R_2, R_3, R_4 and R_5 are as defined above and R_{10} and R_{11} are identical or different lower alkoxy groups; protecting the resulting compound of formula XII



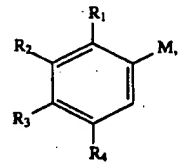
(XII)

at the amino group by an amino-protecting group X_1 and, if desired, reacting the resulting compound of formula XIII



(XIII)

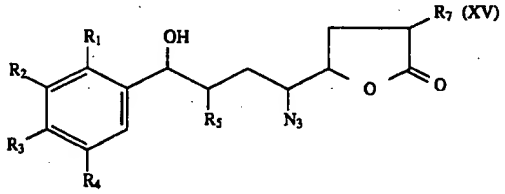
wherein R_9 is formyl, with a compound of formula XIV



(XIV)

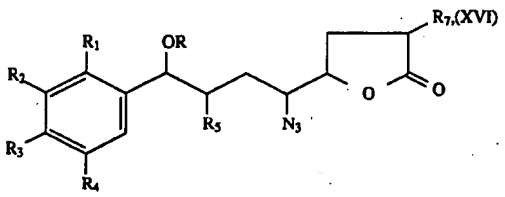
wherein M is a metallic, especially an alkaline earth metallic, radical, for example a group of the formula Mg-Hal

(Hal=halogen, especially bromine), in customary manner, for example in an ethereal solvent, such as tetrahydrofuran, with cooling, for example in a temperature range of approximately from −80° to 0°; if desired temporarily protecting the resulting compound of formula XV



(XV)

at the hydroxy group, for example by reaction with a lower alkanoic acid anhydride, especially isobutyric acid anhydride, in the presence of dimethylaminopyridine in dichloromethane; in the resulting compound of formula XVI

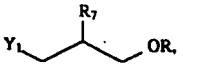


(XVI)

wherein R is hydrogen or a hydroxy-protecting group, such as especially isobutyryl, reducing the azido group to amino, for example by catalytic hydrogenation using palladium-on-carbon, it being possible, if desired, for the group —OR to be replaced reductively by hydrogen, and optionally introducing the protecting group X_1.

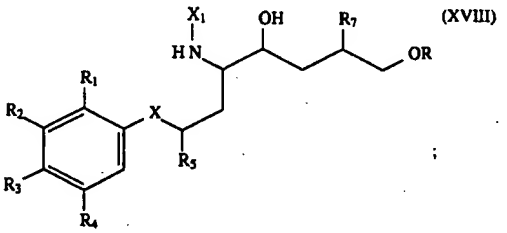
For the preparation of compounds of formula IIa, a compound of formula IIc can be hydrolysed in customary manner with the lactone ring being opened, for example by treatment with lithium hydroxide in a water-containing solvent, for example in DME/water, optionally the hydroxy-protecting group X_3 can be introduced and, if desired, the terminal carboxy group can be reactively modified.

Starting materials of formula IIb are obtained, for example, by reacting a compound of formula XIII wherein R_9 is formyl with a compound of formula XVII



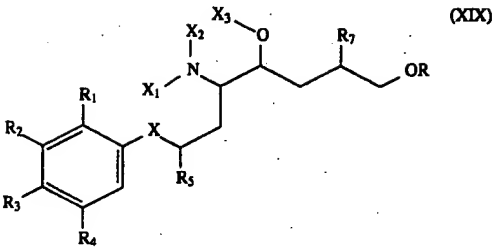
(XVII)

wherein Y_1 is a metallic, especially an alkaline earth metallic, radical, for example of the formula —MgHal wherein Hal is bromine, chlorine or iodine, and OR is etherified hydroxy, such as unsubstituted or substituted benzyloxy, to form the corresponding compound of formula XVIII



(XVIII)

protecting that compound at the amino and hydroxy groups, for example by a bivalent protecting group $—X_2—X_3—$, such as lower alkylidene, especially isopropylidene; in the compound of formula XIX thus protected



(XIX)

freeing the terminal hydroxy group reductively and converting the terminal hydroxy-methyl group into formyl, for example by treatment with N-methylmorpholine-N-oxide and tetrabutylammonium perruthenate in chloroform, and oxidising the resulting aldehyde to the acid in customary manner, for example by treatment with potassium permanganate, or oxidising the resulting terminal alcohol directly to the acid by suitable measures, for example by treatment with sodium iodate/ruthenium chloride, and in each case, if desired, reactively modifying the carboxy function.

Process variant b) (Reduction of lower alkylidene or aryl-lower alkylidene R'_7 to lower alkyl or aryl-lower alkyl R_7).

In a starting material of formula IV, functional groups that are not to participate in the reaction are protected by suitable protecting groups mentioned under a).

Hydrogenation agents suitable for the hydrogenation of the olefinic double bond are those which under the reaction conditions of the process reduce the double bond selectively or more rapidly than the amide bonds present in compounds of formula IV.

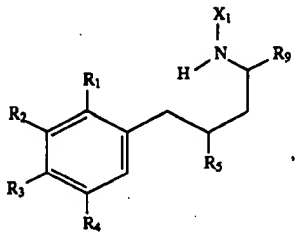
Especially suitable are hydrogenation agents such as hydrogen in the presence of suitable catalysts.

Catalysts suitable for hydrogenation are metals, for example nickel, iron, cobalt or ruthenium, or noble metals or their oxides, such as palladium or rhodium or their oxides, optionally supported on a suitable carrier, such as barium sulfate, aluminium oxide or active carbon, or in the form of skeleton catalysts, for example Raney nickel, but especially homogeneous or heterogeneous metal- or noble metal-ligand complexes, more especially those which produce the configuration at the carbon atom carrying the group R_4 desired in each particular case.

Such catalysts are especially complexes of ruthenium or ruthenium salts, such as Ru(II) halides, such as $RuCl_2$, Ru_2Cl_2 or RuHCl, optionally halogenated Ru(II) lower alkanoylates, such as $Ru(OAc)_2$ or $Ru(OOC—CF_3)_2$, with (S)-bis(2,2'-diphenylphosphino)-1,1'-bi-naphthyl (S-BINAP) or derivatives thereof which contain instead of phenyl substituted phenyl radicals, such as p-tolyl or p-methoxyphenyl, and also ruthenium complexes with (S)-bis(2,2'-diphenylphosphino)-5,5'-dimethyl-diphenyl and the like. Hydrogenation with complexes of that type is preferably carried out in alcohols, such as lower alkanols, or alkyl halides, such as methylene chloride, in a pressure range of approximately from 1 to 100 bar, preferably from 20 to 30 bar, and in a temperature range of approximately from 10° to 80° C., preferably from 15° to 25° C.

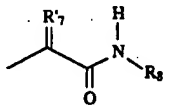
Other solvents customarily used for catalytic hydrogenation are polar organic or inorganic solvents, for example water, alcohols, esters, dioxane, glacial acetic acid or mixtures of those solvents. The hydrogenation is carried out at temperatures of from 0° C. to 250° C., preferably from room temperature to about 100° C. and at hydrogen pressures of from 1 to 200 bar. Hydrogenation methods will be found, for example, in "Organikum, organisch-chemisches Grundpraktikum", 17th revised edition, VEB Deutscher Verlag der Wissenschaften, Berlin 1988.

Carboxylic acid amides of formula IV are obtained, for example, by condensing an aldehyde of formula XIII



(XIII)

wherein R_9 is formyl, in customary manner with a suitable metallated amide compound, for example obtainable by reaction of a compound of formula XX



(XX)

with butyllithium and chlorotitanium triisopropyl oxide.

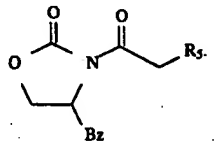
Process variant c) (Reduction of the azido group):

In starting materials of formula V, functional groups that are not to participate in the reaction are protected by one of the protecting groups mentioned under Process a).

Reducing agents suitable for the reduction of the azido group are those which under the reaction conditions of the process reduce an optionally functionalised hydroxy group or azido group selectively or more rapidly than the amide groups present in compounds of formula I.

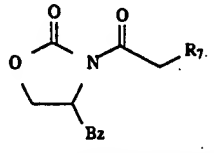
The reduction is preferably carried out with hydrogen in the presence of suitable heavy metal catalysts, for example Raney nickel or platinum or palladium catalysts, for example platinum or palladium on active carbon.

Intermediates of formula V can be prepared, for example, by reacting E-1,4-dibromobut- 2-ene first with a compound of formula VII



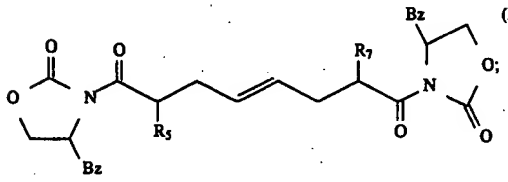
(VII)

and then with a compound of formula XXI



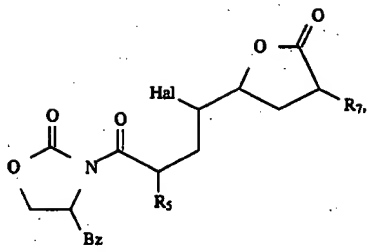
(XXI)

to form the corresponding compound of formula XXII



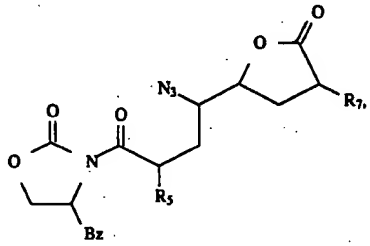
(XXII)

converting that compound, for example by treatment with a customary halogenating agent, such as elemental halogen, especially bromine or iodine, or preferably with an N-halosuccinimide, especially N-bromosuccinimide, in 1,2-dimethoxyethane (DME), into the corresponding compound of formula XXIII



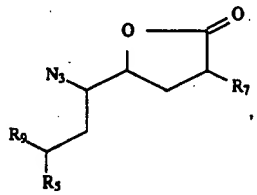
(XXIII)

wherein Hal is halogen; separating the desired isomer in respect of R_5 and R_7 and in that isomer replacing the halogen atom by azido, for example by treatment with tetrabenzylammonium azide in toluene, and in the resulting compound of formula XXIV



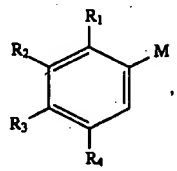
(XXIV)

wherein R_5 and R_7 are as defined above and Bz is benzyl, hydrolysing the 4-benzyl- 2-oxo-oxazolidin-1-ylcarbonyl group selectively to carboxy, for example by treatment with an alkali metal hydroxide in the presence of a basic hydrolysing agent, especially lithium hydroxide in the presence of hydrogen peroxide; re-closing, using an acid catalyst, a lactone ring which may have been opened; in the resulting compound of formula XXV



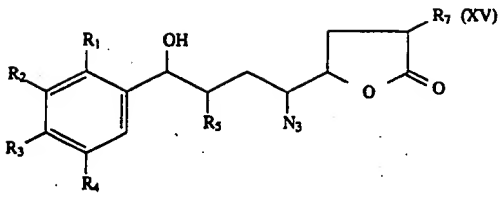
(XXV)

wherein R_9 is carboxy, converting the carboxy group into formyl, for example by conversion into the acid chloride by means of oxalyl chloride and subsequent reduction of the chlorocarbonyl group, for example with sodium tri-tert-butyloxyaluminium hydride in tetrahydrofuran; reacting the resulting compound of formula XXV wherein R_9 is then formyl with a compound of formula XIV

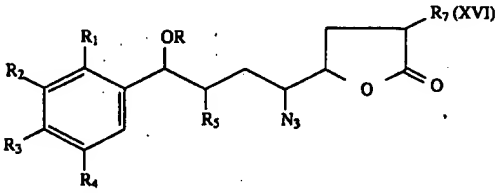


(XIV)

wherein M is a metallic, especially an alkaline earth metallic, radical, for example a group of the formula Mg-Hal (Hal=halogen, especially bromine), in customary manner, for example in an ethereal solvent, such as tetrahydrofuran, with cooling, for example in a temperature range of approximately from −80° to 0° C.; if desired etherifying or, especially, esterifying the resulting compound of formula XV



at the hydroxy group, for example temporarily protecting the hydroxy group by reaction with a lower alkanoic acid anhydride, especially isobutyric acid anhydride, in the presence of dimethylaminopyridine in dichloromethane; reacting the resulting compound of formula XVI



wherein the group —OR is a free or esterified or etherified hydroxy group, with R preferably being a hydroxy-protecting group, such as especially isobutyryl, in customary manner, for example as indicated under Process variant a), with an amine of formula III

$$H_2N—R_8 \qquad (III),$$

wherein R_8 has one of the meanings given under formula I, and, if desired, freeing hydroxymethyl from the group —OR or replacing the group —OR reductively by hydrogen.

The removal of protecting groups that are not constituents of the desired end product of formula I, for example carboxy-, amino-, hydroxy- and/or mercapto-protecting groups, which may be carried out subsequent to the process variants described above, is effected in a manner known per se, for example by means of solvolysis, especially hydrolysis, alcoholysis or acidolysis, or by means of reduction, especially hydrogenolysis or chemical reduction, as well as photolysis, as appropriate stepwise or simultaneously, it being possible also to use enzymatic methods. The removal of the protecting groups is described, for example, in the standard works mentioned hereinabove in the section relating to protecting groups.

For example, protected carboxy, for example tertiary lower alkoxycarbonyl, lower alkoxycarbonyl substituted in the 2-position by a trisubstituted silyl group or in the 1-position by lower alkoxy or by lower alkylthio, or unsubstituted or substituted diphenylmethoxycarbonyl can be converted into free carboxy by treatment with a suitable acid, such as formic acid or trifluoroacetic acid, where appropriate with the addition of a nucleophilic compound, such as phenol or anisole. Unsubstituted or substituted benzyloxycarbonyl can be freed, for example, by means of hydrogenolysis, i.e. by treatment with hydrogen in the presence of a metal hydrogenation catalyst, such as a palladium catalyst. In addition, suitably substituted benzyloxycarbonyl, such as 4-nitrobenzyloxycarbonyl, can be converted into free carboxy also by reduction, for example by treatment with an alkali metal dithionite, such as sodium dithionite, or with a reducing metal, for example zinc, or a reducing metal salt, such as a chromium(II) salt, for example chromium(II) chloride, customarily in the presence of a hydrogen-yielding agent that, together with the metal, is capable of producing nascent hydrogen, such as an acid, especially a suitable carboxylic acid, such as an unsubstituted or substituted, for example hydroxy-substituted, lower alkanecarboxylic acid, for example acetic acid, formic acid, glycolic acid, diphenylglycolic acid, lactic acid, mandelic acid, 4-chloromandelic acid or tartaric acid, or in the presence of an alcohol or thiol, water preferably being added. By treatment with a reducing metal or metal salt, as described above, 2-halo-lower alkoxycarbonyl (where appropriate after conversion of a 2-bromo-lower alkoxycarbonyl group into a corresponding 2-iodo-lower alkoxycarbonyl group) or aroylmethoxycarbonyl can also be converted into free carboxy. Aroylmethoxycarbonyl can be cleaved also by treatment with a nucleophilic, preferably salt-forming, reagent, such as sodium thiophenolate or sodium iodide. 2-(Tri-substituted silyl)-lower alkoxycarbonyl, such as 2-tri-lower alkylsilyl-lower alkoxycarbonyl, can be converted into free carboxy also by treatment with a salt of hydrofluoric acid that yields the fluoride anion, such as an alkali metal fluoride, for example sodium or potassium fluoride, where appropriate in the presence of a macrocyclic polyether ("crown ether"), or with a fluoride of an organic quaternary base, such as tetra-lower alkyl-ammonium fluoride or tri-lower alkylarylammonium fluoride, for example tetraethylammonium fluoride or tetrabutylammonium fluoride, in the presence of an aprotic, polar solvent, such as dimethyl sulfoxide or N,N-dimethylacetamide. Carboxy protected in the form of organic silyloxycarbonyl, such as tri-lower alkylsilyloxycarbonyl, for example trimethylsilyloxycarbonyl, can be freed in customary manner by solvolysis, for example by treatment with water, an alcohol or an acid, or, furthermore, a fluoride, as described above. Esterified carboxy can also be freed enzymatically, for example by means of esterases or suitable peptidases.

A protected amino group is freed in a manner known per se and, according to the nature of the protecting groups, in various ways, preferably by solvolysis or reduction. 2-Halo-lower alkoxycarbonylamino (where appropriate after conversion of a 2-bromo-lower alkoxycarbonylamino group into a 2-iodo-lower alkoxycarbonylamino group), aroylmethoxycarbonylamino or 4-nitrobenzyloxycarbonylamino can be cleaved, for example, by treatment with a suitable reducing agent, such as zinc in the presence of a suitable carboxylic acid, such as aqueous acetic acid. Aroylmethoxycarbonylamino can be cleaved also by treatment with a nucleophilic, preferably salt-forming, reagent, such as sodium thiophenolate, and 4-nitrobenzyloxycarbonylamino also by treatment with an alkali metal dithionite, for example sodium dithionite. Unsubstituted or substituted diphenylmethoxycarbonylamino, tert-lower alkoxycarbonylamino or 2-(tri-substituted silyl)-lower alkoxycarbonylamino, such as 2-tri-lower alkylsilyl-lower alkoxycarbonylamino, can be cleaved by treatment with a suitable acid, for example formic or trifluoroacetic acid; unsubstituted or substituted benzyloxycarbonylamino can be cleaved, for example, by means of hydrogenolysis, i.e. by treatment with hydrogen in the presence of a suitable hydrogenation catalyst, such as a palladium catalyst; unsubstituted or substituted triarylmethylamino or formylamino can be cleaved, for example, by treatment with an acid, such as a mineral acid, for example hydrochloric acid, or an organic acid, for example formic, acetic or trifluoroacetic acid, where appropriate in the presence of water; and an amino group protected in the form of silylamino can be freed, for example, by means of hydrolysis or alcoholysis. An amino group protected by 2-haloacetyl, for example 2-chloroacetyl, can be freed by treatment with thiourea in the presence of a base, or with a thiolate salt, such as an alkali metal thiolate of thiourea, and subsequent solvolysis, such as alcoholysis or hydrolysis, of the resulting

condensation product. An amino group protected by 2-(tri-substituted silyl)-lower alkoxycarbonyl, such as 2-tri-lower alkylsilyl-lower alkoxycarbonyl, can be converted into the free amino group also by treatment with a salt of hydrofluoric acid that yields fluoride anions, as indicated above in connection with the freeing of a correspondingly protected carboxy group. Likewise, silyl, such as trimethylsilyl, bonded directly to a hetero atom, such as nitrogen, can be removed using fluoride ions.

Amino protected in the form of an azido group is converted into free amino, for example, by reduction, for example by catalytic hydrogenation with hydrogen in the presence of a hydrogenation catalyst, such as platinum oxide, palladium or Raney nickel, by reduction using mercapto compounds, such as dithiothreitol or mercaptoethanol, or by treatment with zinc in the presence of an acid, such as acetic acid. The catalytic hydrogenation is preferably carried out in an inert solvent, such as a halogenated hydrocarbon, for example methylene chloride, or in water or in a mixture of water and an organic solvent, such as an alcohol or dioxane, at approximately from 20° C. to 25° C., or with cooling or heating.

A hydroxy or mercapto group protected by a suitable acyl group, by a tri-lower alkylsilyl group or by unsubstituted or substituted 1-phenyl-lower alkyl is freed analogously to a correspondingly protected amino group. A hydroxy or mercapto group protected by 2,2-dichloroacetyl is freed, for example, by basic hydrolysis, and a hydroxy or mercapto group protected by tertiary lower alkyl or by a 2-oxa- or 2-thia-aliphatic or -cycloaliphatic hydrocarbon radical is removed by acidolysis, for example by treatment with a mineral acid or a strong carboxylic acid, for example trifluoroacetic acid. Mercapto protected by pyridyldiphenylmethyl can be freed, for example, using mercury(H) salts at pH 2–6 or by zinc/acetic acid or by electrolytic reduction; acetamidomethyl and isobutyrylamidomethyl can be removed, for example, by reaction with mercury(H) salts at pH 2–6; 2-chloroacetamidomethyl can be removed, for example, using 1-piperidinothiocarboxamide; and S-ethylthio, S-tert-butylthio and S-sulfo can be cleaved, for example, by thiolysis with thiophenol, thioglycolic acid, sodium thiophenolate or 1,4-dithiothreitol. Two hydroxy groups or an adjacent amino and hydroxy group which are protected together by means of a bivalent protecting group, preferably, for example, by a methylene group mono- or di-substituted by lower alkyl, such as lower alkylidene, for example isopropylidene, cyclo-alkylidene, for example cyclohexylidene, or benzylidene, can be freed by acid solvolysis, especially in the presence of a mineral acid or a strong organic acid. 2-Halo-lower alkoxycarbonyl is also removed using the above-mentioned reducing agents, for example a reducing metal, such as zinc, reducing metal salts, such as chromium(II) salts, or using sulfur compounds, for example sodium dithionite or preferably sodium sulfide and carbon disulfide.

When several protected functional groups are present, if desired the protecting groups may be so selected that more than one such group can be removed simultaneously, for example by acidolysis, such as by treatment with trifluoroacetic acid, or with hydrogen and a hydrogenation catalyst, such as a palladium-on-carbon catalyst. Conversely, the groups may also be so selected that they are not all removed simultaneously, but rather they are removed in a desired sequence or only some of them are removed.

In each of the processes mentioned above, the starting compounds may also be used in the form of salts, provided that the reaction conditions allow it.

Compounds of formula I obtainable in accordance with the process can be converted into different compounds of formula I in customary manner.

For example, in a compound of formula I obtainable in accordance with the process, hydroxymethyl X can be reduced reductively to methylene, for example by catalytic hydrogenation in the presence of palladium-on-carbon.

Futhermore, in a compound of formula I obtainable in accordance with the process, a carboxy group in free or reactive form may be esterified or amidated or an esterified or amidated carboxy group may be converted into a free carboxy group.

For the esterification or amidation of a carboxy group in a compound of formula I, if desired the free acid can be used or the free acid can be converted into one of the above-mentioned reactive derivatives and reacted with an alcohol, with ammonia, or with a primary or secondary amine, or, in the case of esterification, the free acid or a reactive salt, for example the caesium salt, can be reacted with a reactive derivative of an alcohol. For example the caesium salt of a carboxylic acid can be reacted with a halide or sulfonic acid ester corresponding to the alcohol. The esterification of the carboxy group can also be carried out with other customary alkylating agents, for example with diazomethane, Meerwein salts or 1-substituted 3-aryltriazenes.

For the conversion of an esterified or amidated carboxy group into the free carboxy group it is possible to use one of the methods described above for the removal of carboxy-protecting groups or, if desired, alkaline hydrolysis in accordance with the reaction conditions mentioned in Organikum, 17th edition, VEB Deutscher Verlag der Wissenschaften, Berlin 1988.

In a compound of formula I obtainable in accordance with the process, an esterified carboxy group can be converted into an unsubstituted or substituted carboxamide group by aminolysis with ammonia or with a primary or secondary amine, optionally in the presence of a suitable condensation agent or catalyst. The aminolysis can be carried out in accordance with the reaction conditions mentioned for such reactions in Organikum, 15th edition, VEB Deutscher Verlag der Wissenschaften, Berlin (East) 1976.

A free amino group present in a compound of formula I obtainable in accordance with the process can be acylated or alkylated, for example to introduce a radical R_6 other than hydrogen. The acylation and the alkylation can be carded out in accordance with one of the methods mentioned for protecting groups or according to one of the processes mentioned in Organikum, 17th edition, VEB Deutscher Verlag der Wissenschaften, Berlin (East) 1988.

Furthermore, a free hydroxy group present in a compound of formula I obtainable in accordance with the process, for example as a constituent of the radical R_8, can be acylated. The acylation can be carried out with acylating reagents in accordance with one of the methods mentioned for protecting groups or according to one of the processes mentioned in Organikum, 17th edition, VEB Deutscher Verlag der Wissenschaften, Berlin (East) 1988.

In a compound of formula I obtainable in accordance with the process it is also possible to obtain from a sulfide the corresponding sulfoxide or sulfone, that is to say to oxidise a thio group to a sulfinyl or sulfonyl group or a sulfinyl group to sulfonyl, and also to oxidise thiomorpholino to S-oxy- or S,S-dioxy-thiomorpholino.

The oxidation to the sulfone can be carried out with most of the customary oxidising agents. It is especially preferable to use oxidising agents that oxidise the thio group or the sulfide sulfur selectively in the presence of other functional

groups, for example amino or hydroxy groups, of the compound of formula I in question, for example aromatic or aliphatic peroxycarboxylic acids, for example peroxybenzoic acid, monoperphthalic acid, m-chloroperbenzoic acid, peracetic acid, performic acid or trifluoroperacetic acid. The oxidation with peroxycarboxylic acids is carried out in suitable solvents customarily used for that purpose, for example chlorinated hydrocarbons, for example methylene chloride or chloroform, ethers, such as diethyl ether, esters, such as ethyl acetate or the like, at temperatures of from −78° C. to room temperature, for example from −20° C. to +1 0° C., preferably about 0° C. The peroxycarboxylic acid can also be formed in situ, for example with hydrogen peroxide in acetic acid or formic acid that optionally contains acetic anhydride, for example with 30% or 90% hydrogen peroxide in acetic acid/acetic anhydride. Other peroxo compounds are also suitable, for example potassium peroxomonosulfate in lower alkanol/water mixtures, for example methanol/water or ethanol/water, or in aqueous acetic acid at temperatures of from −70° C. to +30° C., for example from −20° C. to room temperature, and also sodium metaperiodate in methanol or methanol/water mixtures at temperatures of from 0° C. to 50° C., for example about room temperature. If stoichiometric amounts of the mentioned oxidising agents are used it is also possible to obtain the corresponding sulfoxides.

If desired, it is possible by reduction of a sulfonyl group or a sulfone radical in an obtainable compound of formula I to obtain the corresponding thio compound or the corresponding sulfide, for example with diisobutylaluminium hydride in ether or tetrahydrofuran.

In compounds of formula I it is also possible to replace hydroxy R_1, R_2, R_3 and/or R_4 by one of the etherified hydroxy groups mentioned under formula I by reacting the corresponding compound of formula I wherein R_1, R_2, R_3 and/or R_4 is hydroxy in customary manner, for example in the presence of a basic condensation agent, with a compound of the formula(e) R'_1—Y, R'_2—Y, R'_3—Y and/or R'_4—Y wherein R'_1 is lower alkyl or free or esterified or amidated carboxy-lower alkyl, R'_2 is lower alkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, optionally lower alkanoylated, halogenated or sulfonylated hydroxy-lower alkyl, oxo-lower alkyl, lower alkyl, lower alkenyl, cycloalkoxy-lower alkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkenyl, lower alkenyloxy-lower alkyl, lower alkenyloxy-lower alkyl, lower alkenyloxy-lower alkyl, lower alkanoyl-lower alkyl, optionally S-oxidised lower alkyl-thio-lower alkyl, lower alkylthio-(hydroxy)-lower alkyl, aryl-lower alkyl, optionally hydrogenated heteroaryl-lower alkyl, optionally hydrogenated heteroarylthio-lower alkyl, cyano-lower alkyl or free or esterified or amidated carboxy-lower alkyl, R'_3 is lower alkyl, lower alkoxy-lower alkyl, hydroxy-lower alkyl, aryl-lower alkyl, halogenated lower alkyl, cyano-lower alkyl or free or esterified or amidated carboxy-lower alkyl, and R'_4 is lower alkyl, and Y is reactive esterified hydroxy, especially hydroxy esterified by a mineral acid, by sulfuric acid or by an organic sulfonic acid, such as halogen, preferably chlorine, bromine or iodine, groups of the formula O—SO_2—O—R'_A, or lower alkanesulfonyloxy or unsubstituted or substituted benzenesulfonyloxy, especially methane-, ethane-, benzene-, p-toluene- or p-bromobenzene-sulfonyl. The reaction is, as mentioned, preferably carried out in the presence of a basic condensation agent, such as an alkali metal carbonate, for example potassium carbonate, in an inert solvent, such as a lower alkanol, such as methanol, ethanol, butanol, tert-butanol or especially amyl alcohol, advantageously at elevated temperature, for example in a temperature range of approximately from 40° to 140° C., if necessary with removal of the resulting water of reaction by distillation, for example by azeotropic distillation.

It is also possible for salts of compounds of formula I obtainable in accordance with the process to be converted in a manner known per se into the free compounds, for example by treatment with a base, such as an alkali metal hydroxide, a metal carbonate or metal hydrogen carbonate, or ammonia, or another of the salt-forming bases mentioned at the beginning, or with an acid, such as a mineral acid, for example with hydrochloric acid, or another of the salt-forming acids mentioned at the beginning.

Resulting salts can be converted into different salts in a manner known per se: acid addition salts, for example, by treatment with a suitable metal salt, such as a sodium, barium or silver salt, of a different acid in a suitable solvent in which an inorganic salt being formed is insoluble and is therefore eliminated from the reaction equilibrium, and basic salts by freeing of the free acid and conversion into a salt again.

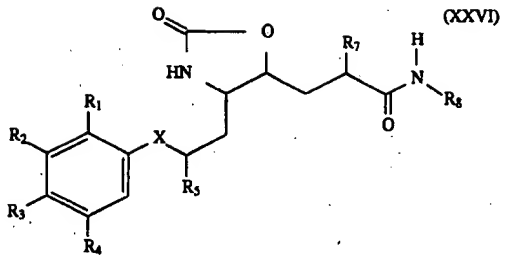
The compounds of formula I, including their salts, may also be obtained in the form of hydrates or may include the solvent used for crystallisation.

As a result of the close relationship between the novel compounds in free form and in the form of their salts, hereinabove and hereinbelow any reference to the free compounds and their salts is to be understood as including also the corresponding salts and free compounds, respectively, as appropriate and expedient.

Stereoisomeric mixtures, that is to say mixtures of diastereoisomers and/or enantiomers, such as, for example, racemic mixtures, can be separated into the corresponding isomers in a manner known per se by suitable separating processes. For example, mixtures of diastereoisomers can be separated into the individual diastereoisomers by fractional crystallisation, chromatography, solvent partition etc.. Racemates can be separated from one another, after conversion of the optical antipodes into diastereoisomers, for example by reaction with optically active compounds, for example optically active acids or bases, by chromatography on column materials charged with optically active compounds or by enzymatic methods, for example by selective reaction of only one of the two enantiomers. This separation can be carried out either at the stage of one of the starting materials or with the compounds of formula I themselves.

In a compound of formula I the configuration at individual chirality centres can be selectively reversed. For example, the configuration of asymmetric carbon atoms that carry nucleophilic substituents, such as amino or hydroxy, can be reversed by second order nucleophilic substitution, optionally after conversion of the bonded nucleophilic substituent into a suitable nucleofugal leaving group and reaction with a reagent introducing the original substituent, or the configuration at carbon atoms having hydroxy groups can be reversed by oxidation and reduction, analogously to European Patent Application EP-A-0 236 734.

Also advantageous is the reactive functional modification of the hydroxy group and the subsequent replacement thereof by hydroxy with the configuration being reversed. For that purpose, the amino and hydroxy groups shown in formula I are bridged by a bivalent group, especially carbonyl, there being obtained a compound of formula XXVI



(XXVI)

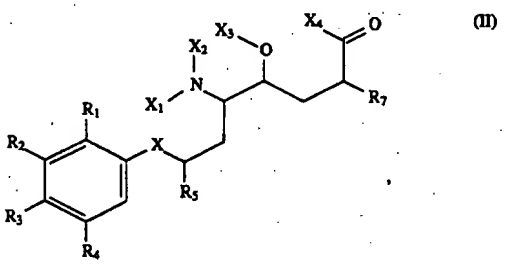
which can be cleaved again by treatment with thionyl chloride with the configuration being reversed.

The invention relates also to those forms of the process in which a compound obtainable as intermediate at any stage is used as starting material and the remaining steps are carried out or the process is interrupted at any stage or a starting material is formed under the reaction conditions or is used in the form of a reactive derivative or salt, or a compound obtainable in accordance with the process of the invention is formed under the process conditions and further processed in situ. It is preferable to use those starting materials which result in the compounds described above as being very preferred or very especially preferred.

The invention relates also to novel starting materials, which have been developed specifically for the preparation of the compounds according to the invention, especially the group of starting materials resulting in the compounds of formula I described at the beginning as being preferred, to processes for their preparation and to their use as intermediates.

This relates to compounds of formula II which, as mentioned, are suitable as intermediates for the preparation of compounds of formula I.

The invention relates accordingly also to compounds of formula II



(II)

wherein

R_1 is hydrogen, hydroxy, lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy or free or esterified or amidated carboxy-lower alkoxy,

R_2 is hydrogen, lower alkyl, cycloalkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, hydroxy, optionally lower alkanoylated, halogenated or sulfonylated hydroxy-lower alkoxy; amino-lower alkyl that is unsubstituted or substituted by lower alkyl-, by lower alkanoyl- and/or by lower alkoxy-carbonyl; amino-lower alkoxy that is substituted by lower alkyl, by lower alkanoyl and/or by lower alkoxycarbonyl; oxo-lower alkoxy, lower alkoxy, cycloalkoxy, lower alkenyloxy, cycloalkoxy-lower alkoxy, lower alkoxy-lower alkoxy, lower alkoxy-lower alkenyl, lower alkenyloxy-lower alkoxy, lower alkoxy-lower alkoxy, lower alkenyloxy-lower alkyl, lower alkanoyl-lower alkoxy, optionally S-oxidised lower alkylthio-lower alkoxy, lower alkylthio-(hydroxy)-lower alkoxy, aryl-lower alkoxy, cyano-lower alkoxy, free or esterified or amidated carboxy-lower alkoxy or free or esterified or amidated carboxy-lower alkyl,

R_3 is optionally halogenated lower alkyl, lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, hydroxy-lower alkyl, optionally S-oxidised lower alkylthio-lower alkyl, optionally hydrogenated heteroaryl-lower alkyl, optionally hydrogenated heteroarylthio-lower alkyl; amino-lower alkyl that is unsubstituted or N-mono- or N,N-di-lower alkylated, N-lower alkanoylated or N-lower alkanesulfonylated or N,N-disubstituted by lower alkylene, by unsubstituted or N'-lower alkylated or N'-lower alkanoylated aza-lower alkylene, by oxa-lower alkylene or by optionally S-oxidised thia-lower alkylene; cyano-lower alkyl, free or esterified or amidated carboxy-lower alkyl, cycloalkyl, aryl, hydroxy, lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy, cycloalkoxy-lower alkoxy, hydroxy-lower alkoxy, aryl-lower alkoxy, optionally halogenated lower alkoxy, optionally S-oxidised lower alkylthio-lower alkoxy, optionally hydrogenated heteroaryl-lower alkoxy, optionally hydrogenated heteroarylthio-lower alkoxy; amino-lower alkoxy that is unsubstituted or N-mono- or N,N-di-lower alkylated, N-lower alkanoylated or N-lower alkanesulfonylated or substituted by lower alkylene, by unsubstituted or N'-lower alkylated or N'-lower alkanoylated aza-lower alkylene, by oxa-lower alkylene or by optionally S-oxidised thia-lower alkylene; cyano-lower alkoxy or free or esterified or amidated carboxy-lower alkoxy, or together with R_4 is lower alkylenedioxy or a fused-on benzo or cyclohexeno ring,

R_4 together with R_3 is lower alkylenedioxy or a fused-on benzo or cyclohexeno ring, or is hydrogen, hydroxy or lower alkoxy,

X is methylene or hydroxymethylene,

R_5 is lower alkyl or cycloalkyl,

R_7 is lower alkyl or aryl-lower alkyl,

X_1 is an amino-protecting group,

X_2 is hydrogen or together with X_3 is a bivalent protecting group,

X_3 is hydrogen, a hydroxy-protecting group or together with X_2 is a bivalent protecting group or together with X_4 is a direct bond, and

X_4 is free or reactively etherified or esterified hydroxy or together with X_3 is a direct bond,

and to the salts thereof, to processes for the preparation thereof and to the use thereof as intermediates for the preparation of medicinal active ingredients, especially of formula I.

In the compounds of formula II prepared according to the invention the variables R_1, R_2, R_3, R_4, X, R_5 and R_7 are preferably as defined for formula I, and the variables X_1, X_2, X_3 and X_4 are preferably as defined for formula II.

The invention relates especially to compounds of formula II wherein

R_1 is hydrogen, hydroxy, lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy, carboxy-lower alkoxy, lower alkoxycarbonyl-lower alkoxy, carbamoyl-lower alkoxy or N-mono- or N,N-di-lower alkylcarbamoyl-lower alkoxy,

R_2 is hydrogen, lower alkyl, cycloalkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, hydroxy, lower alkanoyloxy-lower alkyl, hydroxy-lower alkoxy, halo-(hydroxy)-

lower alkoxy, lower alkanesulfonyl-(hydroxy)-lower alkoxy, amino-lower alkyl, lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl, lower alkanoylamino-lower alkyl, lower alkoxycarbonyl-amino-lower alkyl, amino-lower alkoxy, lower alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy, lower alkanoylamino-lower alkoxy, lower alkoxycarbonyl-amino-lower alkoxy, oxo-lower alkoxy, lower alkoxy, cycloalkoxy, lower alkenyloxy, cycloalkoxy-lower alkoxy, lower alkoxy-lower alkoxy, lower alkoxy-lower alkenyl, lower alkenyloxy-lower alkoxy, lower alkoxy-lower alkoxy, lower alkenyloxy-lower alkyl, lower alkanoyl-lower alkoxy, lower alkylthio-lower alkoxy, lower alkane-sulfonyl-lower alkoxy, lower alkylthio-(hydroxy)-lower alkoxy, aryl-lower alkoxy, thiazolylthio-lower alkoxy or thiazolinylthio-lower alkoxy, imidazolylthio-lower alkoxy, optionally N-oxidised pyridylthio-lower alkoxy, pyrimidinylthio-lower alkoxy, cyano-lower alkoxy, lower alkoxycarbonyl-lower alkoxy, carbamoyl-lower alkoxy, N-mono- or N,N-di-lower alkylcarbamoyl-lower alkoxy, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, carbamoyl-lower alkyl or N-mono- or N,N-di-lower alkylcarbamoyl-lower alkyl,

R_3 is lower alkyl, polyhalo-lower alkyl, lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, hydroxy-lower alkyl, lower alkylthio-lower alkyl, lower alkanesulfonyl-lower alkyl, optionally partially hydrogenated or N-oxidised pyridyl-lower alkyl, thiazolyl-thio-lower alkyl or thiazolinylthio-lower alkyl, imidazolylthio-lower alkyl, optionally N-oxidised pyridylthio-lower alkyl, pyrimidinylthio-lower alkyl, amino-lower alkyl, lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl, lower alkanoyl-amino-lower alkyl, lower alkanesulfonylamino-lower alkyl, polyhalo-lower alkane-sulfonylamino-lower alkyl, pyrrolidino-lower alkyl, piperidino-lower alkyl, piperazino-, N'-lower alkylpiperazino- or N'-lower alkanoylpiperazino-lower alkyl, morpholino-lower alkyl, thiomorpholino-, S-oxothiomorpholino- or S,S-dioxothio-morpholino-lower alkyl, cyano-lower alkyl, carboxy-lower alkyl, lower alkoxy-carbonyl-lower alkyl, carbamoyl-lower alkyl, N-mono- or N,N-di-lower alkyl-carbamoyl-lower alkyl, cycloalkyl; phenyl or naphthyl that is unsubstituted or mono-, di- or tri-substituted by lower alkyl, lower alkoxy, hydroxy, lower alkylamino, di-lower alkylamino, halogen and/or by trifluoromethyl; hydroxy, lower alkoxy, cyclo-alkoxy, lower alkoxy-lower alkoxy, cycloalkoxy-lower alkoxy, hydroxy-lower alkoxy; phenyl-lower alkoxy or naphthyl-lower alkoxy that is unsubstituted or mono-, di- or tri-substituted by lower alkyl, lower alkoxy, hydroxy, lower alkylamino, di-lower alkylamino, halogen and/or by trifluoromethyl; lower alkoxy, polyhalo-lower alkoxy, lower alkylthio-lower alkoxy, lower alkanesulfonyl-lower alkoxy, optionally hydrogenated heteroaryl-lower alkoxy, optionally partially or fully hydrogenated heteroarylthio-lower alkoxy, such as thiazolylthio-lower alkoxy or thiazolinylthio-lower alkoxy, imidazolylthio-lower alkoxy, optionally N-oxidised pyridylthio-lower alkoxy, pyrimidinylthio-lower alkoxy, amino-lower alkoxy, lower alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy, lower alkanoylamino-lower alkoxy, lower alkanesulfonylamino-lower alkoxy, polyhalo-lower alkanesulfonylamino-lower alkoxy, pyrrolidino-lower alkoxy, piperidino-lower alkoxy, piperazino-, N'-lower alkylpiperazino- or N'-lower alkanoylpiperazino-lower alkoxy, morpholino-lower alkoxy, thiomorpholino-, S-oxothiomorpholino- or S,S-dioxothiomorpholino-lower alkoxy, cyano-lower alkoxy, carboxy-lower alkoxy, lower alkoxycarbonyl-lower alkoxy, carbamoyl-lower alkoxy or N-mono- or N,N-di-lower alkylcarbamoyl-lower alkoxy, or together with R_4 is lower alkylenedioxy or a fused-on benzo or cyclohexeno ring,

R_4 together with R_3 is lower alkylenedioxy or a fused-on benzo or cyclohexeno ring, or is hydrogen, hydroxy or lower alkoxy,

X is methylene or hydroxymethylene,

R_5 is lower alkyl or cycloalkyl,

R_7 is lower alkyl, or phenyl-lower alkyl that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen, nitro and/or by amino,

X_1 is lower alkoxycarbonyl, or α-phenyl- or α,α-diphenyl-lower alkoxycarbonyl that is unsubstituted or substituted by lower alkyl, lower alkoxy, nitro and/or by halogen, or is 2-halo-lower alkoxycarbonyl,

X_2 is hydrogen or together with X_3 is carbonyl or lower alkylidene,

X_3 is hydrogen, tri-lower alkylsilyl or together with X_2 is carbonyl or lower alkylidene or together with X_4 is a direct bond, and

X_4 is lower alkoxy, phenyl-lower alkoxy or hydroxy or together with X_3 is a direct bond,

and the salts thereof.

The invention relates more especially to compounds of formula II wherein

R_1 is hydrogen,

R_2 is lower alkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkoxy, lower alkoxy-lower alkoxy-lower alkyl; phenyl-lower alkoxy that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen, nitro and/or by amino; optionally N-oxidised pyridyl-lower alkoxy, lower alkylthio-lower alkoxy, lower alkane-sulfonyl-lower alkoxy, lower alkanoyl-lower alkoxy, optionally N-oxidised pyridyl-lower alkoxy, cyano-lower alkoxy, carboxy-lower alkoxy, lower alkoxycarbonyl-lower alkoxy, carbamoyl-lower alkoxy, lower alkylcarbamoyl-lower alkoxy or di-lower alkylcarbamoyl-lower alkoxy,

R_3 is hydrogen, lower alkyl, hydroxy, lower alkoxy or polyhalo-lower alkoxy or together with R_4 is lower alkylenedioxy,

X is methylene or hydroxymethylene,

R_5 is lower alkyl or cycloalkyl,

R_7 is lower alkyl,

X_1 is lower alkoxycarbonyl, or α-phenyl-lower alkoxycarbonyl that is unsubstituted or substituted by lower alkyl, lower alkoxy, nitro and/or by halogen,

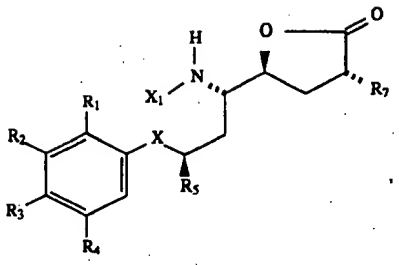
X_2 is hydrogen or together with X_3 is lower alkylidene,

X_3 is hydrogen or together with X_2 is lower alkylidene or together with X_4 is a direct bond, and

X_4 is hydroxy or together with X_3 is a direct bond,

and the salts thereof.

The invention relates especially to compounds of formula II wherein at least one, for example one, two or preferably all, of the asymmetric carbon atoms of the main chain have the stereochemical configuration shown in formula IId


(IId)

the variables each being as defined above, and the salts thereof.

The invention relates very especially to compounds of formula IId wherein

R_1 and R_4 are hydrogen,

R_2 is C_1–C_4alkoxy-C_1–C_4alkoxy, such as 3-methoxypropyloxy, or C_1–C_4alkoxy-C_1–C_4-alkyl, such as 3-methoxybutyl,

R_3 is C_1–C_4alkyl, such as isopropyl or tert-butyl, or C_1–C_4alkoxy, such as methoxy,

X is methylene,

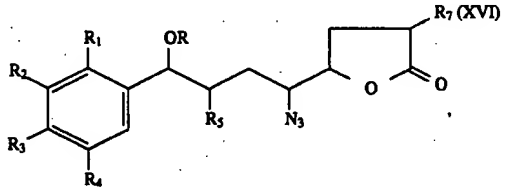
R_5 and R_7 are branched C_1–C_4alkyl, such as isopropyl, and

X_1 is C_1–C_7alkoxycarbonyl, such as tert-butoxycarbonyl, and the salts thereof.

The invention relates specifically to the compounds of formulae II and IId mentioned in the Examples and the salts thereof.

The process according to the invention for the preparation of compounds of formula II is as follows:

d) for the preparation of compounds of formula IIc, in a compound of formula XVI

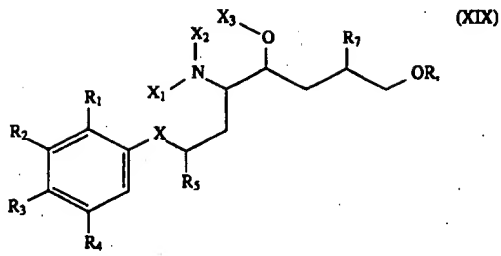

(XVI)

wherein

R is a hydroxy-protecting group, the azido group is reduced to amino and, if desired, hydroxy is freed from the group —OR or the group —OR is replaced reductively by hydrogen, and the protecting group X_1 is introduced, and

e) for the preparation of compounds of formula IIa, a compound of formula IIc is hydrolysed in customary manner, the hydroxy-protecting group X_3 is introduced and, if desired, the terminal carboxy group is reactively modified, or

f) for the preparation of compounds of formula IIb, in a compound of formula XIX


(XIX)

the terminal hydroxy group is freed reductively and the terminal hydroxymethyl group is first converted into formyl in customary manner, for example as indicated under Process variant a), and the formyl group formed is oxidised to the acid in customary manner or the terminal hydroxy group is oxidised directly to the acid, and, if desired, the carboxy function is reactively modified, if necessary any protecting groups present are removed and, if desired, the compound obtainable in accordance with the process is converted into a salt or a salt obtainable in accordance with the process is converted into the free compound or into a different salt and/or mixtures of isomers that may be obtainable are separated.

The starting materials of formulae XVI and XIX are prepared, for example, as indicated under Process variant a).

Compounds of formula II obtainable in accordance with the process can be converted into different compounds of formula II in customary manner.

For example, in a compound of formula II obtainable in accordance with the process, hydroxymethyl X can be reduced reductively to methylene, for example by catalytic hydrogenation in the presence of palladium-on-carbon.

Furthermore, in a compound of formula II obtainable in accordance with the process, a carboxy group in free or reactive form may be esterified or amidated or an esterified or amidated carboxy group may be converted into a free carboxy group.

For the esterification or amidation of a carboxy group in a compound of formula II, if desired the free acid can be used or the free acid can be converted into one of the above-mentioned reactive derivatives and reacted with an alcohol, with ammonia, or with a primary or secondary amine, or in the case of esterification, the free acid or a reactive salt, for example the caesium salt, can be reacted with a reactive derivative of an alcohol. For example the caesium salt of a carboxylic acid can be reacted with a halide or sulfonic acid ester corresponding to the alcohol. The esterification of the carboxy group can also be carried out using other customary alkylating agents, for example with diazomethane, Meerwein salts or 1-substituted 3-aryltriazenes.

For the conversion of an esterified or amidated carboxy group into the free carboxy group it is possible to use one of the methods described above for the removal of carboxy-protecting groups or, if desired, alkaline hydrolysis in accordance with the reaction conditions mentioned in Organikum, 17th edition, VEB Deutscher Verlag der Wissenschaften, Berlin 1988.

In compounds of formula II it is also possible to replace hydroxy R_1, R_2, R_3 and/or R_4 by one of the etherified hydroxy groups mentioned under formula II by reacting the corresponding compound of formula II wherein R_1, R_2, R_3 and/or R_4 is hydroxy in customary manner, for example in the presence of a basic condensation agent, with a compound of the formula(e) R'_1—Y, R'_2—Y, R'_3—Y and/or R'_4—Y wherein R'_1 is lower alkyl or free or esterified or amidated carboxy-lower alkyl, R'_2 is lower alkyl, lower alkoxy-lower

alkyl, lower alkoxy-lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, optionally lower alkanoylated, halogenated or sulfonylated hydroxy-lower alkyl, oxo-lower alkyl, lower alkyl, lower alkenyl, cycloalkoxy-lower alkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkenyl, lower alkenyloxy-lower alkyl, lower alkenyloxy-lower alkyl, lower alkenyloxy-lower alkyl, lower alkanoyl-lower alkyl, optionally S-oxidised lower alkyl-thio-lower alkyl, lower alkylthio-(hydroxy)-lower alkyl, aryl-lower alkyl, optionally hydrogenated heteroaryl-lower alkyl, optionally hydrogenated heteroarylthio-lower alkyl, cyano-lower alkyl or free or esterified or amidated carboxy-lower alkyl, R'_3 is lower alkyl, lower alkoxy-lower alkyl, hydroxy-lower alkyl, aryl-lower alkyl, halogenated lower alkyl, cyano-lower alkyl or free or esterified or amidated carboxy-lower alkyl, and R'_4 is lower alkyl, and Y is reactive esterified hydroxy, especially hydroxy esterified by a mineral acid, by sulfuric acid or by an organic sulfonic acid, such as halogen, preferably chlorine, bromine or iodine, groups of the formula $O—SO_2—O—R'_4$, or lower alkanesulfonyloxy or unsubstituted or substituted benzenesulfonyloxy, especially methane-, ethane-, benzene-, p-toluene- or p-bromobenzene-sulfonyl. The reaction is, as mentioned, preferably carried out in the presence of a basic condensation agent, such as an alkali metal carbonate, for example potassium carbonate, in an inert solvent, such as a lower alkanol, such as methanol, ethanol, butanol, tert-butanol or especially amyl alcohol, advantageously at elevated temperature, for example in a temperature range of approximately from 40° to 140° C., if necessary with removal of the resulting water of reaction by distillation, for example by azeotropic distillation.

It is also possible for salts of compounds of formula II obtainable in accordance with the process to be converted in a manner known per se into the free compounds, for example by treatment with a base, such as an alkali metal hydroxide, a metal carbonate or metal hydrogen carbonate, or ammonia, or another of the salt-forming bases mentioned at the beginning, or with an acid, such as a mineral acid, for example with hydrochloric acid, or another of the salt-forming acids mentioned at the beginning.

Resulting salts can be convened into different salts in a manner known per se: acid addition salts, for example, by treatment with a suitable metal salt, such as a sodium, barium or silver salt, of a different acid in a suitable solvent in which an inorganic salt being formed is insoluble and is therefore eliminated from the reaction equilibrium, and basic salts by freeing of the free acid and conversion into a salt again.

The compounds of formula II, including their salts, may also be obtained in the form of hydrates or may include the solvent used for crystallisation.

As a result of the close relationship between the novel compounds in free form and in the form of their salts, hereinabove and hereinbelow any reference to the free compounds and their salts is to be understood as including also the corresponding salts and free compounds, respectively, as appropriate and expedient.

The invention relates also to pharmaceutical compositions comprising compounds of formula I.

The pharmacologically acceptable compounds of the present invention may be used, for example, in the preparation of pharmaceutical compositions that comprise an effective amount of the active ingredient together or in admixture with a significant amount of inorganic or organic, solid or liquid, pharmaceutically acceptable carriers.

The pharmaceutical compositions according to the invention are compositions for enteral, such as nasal, rectal or oral, or parenteral, such as intramuscular or intravenous, administration to warm-blooded animals (human beings and animals) that comprise an effective dose of the pharmacological active ingredient alone or together with a significant amount of a pharmaceutically acceptable carrier. The dose of the active ingredient depends on the species of warm-blooded animal, body weight, age and individual condition, individual pharmacokinetic data, the disease to be treated and the mode of administration.

The pharmaceutical compositions comprise from approximately 1% to approximately 95%, preferably from approximately 20% to approximately 90%, active ingredient. Pharmaceutical compositions according to the invention may be, for example, in unit dose form, such as in the form of ampoules, vials, suppositories, dragées, tablets or capsules.

The pharmaceutical compositions of the present invention are prepared in a manner known per se, for example by means of conventional dissolving, lyophilising, mixing, granulating or confectioning processes.

Solutions of the active ingredient, and also suspensions, and especially isotonic aqueous solutions or suspensions, are preferably used, it being possible, for example in the case of lyophilised compositions that comprise the active ingredient alone or together with a carrier, for example mannitol, for such solutions or suspensions to be made up prior to use. The pharmaceutical compositions may be sterilised and/or may comprise excipients, for example preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers, and are prepared in a manner known per se, for example by means of conventional dissolving or lyophilising processes. The said solutions or suspensions may comprise viscosity-increasing substances, such as sodium carboxymethylcellulose, carboxymethylcellulose, dextran, polyvinylpyrrolidone or gelatin.

Suspensions in oil comprise as the oil component the vegetable, synthetic or semi-synthetic oils customary for injection purposes. There may be mentioned as such especially liquid fatty acid esters that contain as the acid component a long-chained fatty acid having from 8 to 22, especially from 12 to 22, carbon atoms, for example lauric acid, tridecylic acid, myristic acid, pentadecylic acid, palmitic acid, margaric acid, stearic acid, arachidic acid, behenic acid or corresponding unsaturated acids, for example oleic acid, elaidic acid, erucic acid, brassidic acid or linoleic acid, if desired with the addition of antioxidants, for example vitamin E, β-carotene or 3,5-di-tert-butyl-4-hydroxytoluene. The alcohol component of those fatty acid esters has a maximum of 6 carbon atoms and is a mono- or poly-hydric, for example a mono-, di- or tri-hydric, alcohol, for example methanol, ethanol, propanol, butanol or pentanol or the isomers thereof, but especially glycol and glycerol. The following examples of fatty acid esters are therefore to be mentioned: ethyl oleate, isopropyl myristate, isopropyl palmitate, "Labrafil M 2375" (polyoxyethylene glycerol trioleate, Gattefossé, Paris), "Miglyol 812" (triglyceride of saturated fatty acids with a chain length of C_8 to C_{12}, Chemische Werke Witten/Ruhr, Germany), but especially vegetable oils, such as cottonseed oil, almond oil, olive oil, castor oil, sesame oil, soybean oil and more especially groundnut oil.

The injection compositions are prepared in customary manner under sterile conditions; the same applies also to introducing the compositions into ampoules or vials and sealing the containers.

Pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with solid

carriers, if desired granulating a resulting mixture, and processing the mixture, if desired or necessary, after the addition of appropriate excipients, into tablets, dragée cores or capsules. They can also be incorporated into plastics carriers that allow the active ingredients to diffuse or be released in measured amounts.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starch pastes using, for example, corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxy-methyl starch, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate. Excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable, optionally enteric, coatings, there being used, inter alia, concentrated sugar solutions which may comprise gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents, or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as ethylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Capsules are dry-filled capsules made of gelatin and also soft, sealed capsules made of gelatin and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may comprise the active ingredient in the form of granules, for example with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and if desired with stabilisers. In soft capsules the active ingredient is preferably dissolved or suspended in suitable oily excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols, it likewise being possible for stabilisers and/or antibacterial agents to be added. Dyes or pigments may be added to the tablets or dragée coatings or to the capsule casings, for example for identification purposes or to indicate different doses of active ingredient.

The invention relates also to the use of compounds of formula I in the treatment of disorders responsive to the inhibition of renin, such as those mentioned at the beginning, especially hypertension and/or glaucoma.

The doses to be administered to warm-blooded animals, for example human beings, of, for example, approximately 70 kg body weight, especially the doses effective in the inhibition of the enzyme renin, in lowering blood pressure and/or in improving the symptoms of glaucoma, are from approximately 3 mg to approximately 3 g, preferably from approximately 10 mg to approximately 1 g, for example approximately from 20 mg to 200 mg, per person per day, divided preferably into 1 to 4 single doses which may, for example, be of the same size. Usually, children receive about half of the adult dose. The dose necessary for each individual can be monitored, for example by measuring the serum concentration of the active ingredient, and adjusted to an optimum level.

The following Examples serve to illustrate the invention; temperatures are given in degrees Celsius, pressures in mbar.

HPLC—column dimensions: 250×4.6 mm

HPLC—column packing: Nucleosil® $5C_{18}$

HPLC—eluants: A) water+0.1% by vol. trifluoroacetic acid B) acetonitrile+0. 1% by vol. trifluoroacetic acid

HPLC—gradient 0: 20–100% B in 20 minutes+8 minutes 100% B

HPLC—gradient I: linear in 60 minutes from 30% by vol. B+70% by vol. A to 90% by vol. B + 10% by vol. A

The abbreviation "R_f(A)" means, for example, that the R_f value was determined in solvent system A. The quantity ratio of solvents to one another is always given in parts by volume.

The same abbreviations are used for indicating the eluant systems for flash chromatography and medium pressure chromatography.

Mass-spectroscopic measurements are obtained either by conventional MS or in accordance with the "Fast-Atom-Bombardment" (FAB-MS) method. In the former case the mass data relate to the unprotonated molecule ion $(M)^+$ or the protonated molecule ion $(M+H)^+$.

The short names and abbreviations used have the following meanings:

C_{18}-Nucleosil® brand name for reversed phase column material for HPLC charged with octadecyl radicals (Nucleosil® $5C_{18}$, Macherey & Nagel, FRG)

pFAB-MS Fast-Atom-Bombardment mass spectroscopy

FC flash chromatography

HPLC high performance liquid chromatography

Hyflo® brand name for filter aids (Fluka, Buchs, Switzerland)

IR infrared spectroscopy

b.p. at the pressure indicated in torr

ml milliliters

MS mass spectroscopy

R_f ratio of the migration of a substance to the distance of the eluant front from the starting point in TLC

R_t retention time of a substance in HPLC (in minutes)

m.p. melting point (temperature).

EXAMPLE 1

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(p-tert-butylphenyl)-octanoic acid (N-butyl)amide hydrochloride

111 mg of N-tert-butoxycarbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl- 8-(p-tert-butyl-phenyl)-octanoic acid (N-butyl)amide are dissolved in 2 ml of 4N hydrochloric acid in dioxane at 0° C. and then stirred for 60 minutes at 20° C. The reaction mixture is concentrated by evaporation under reduced pressure and the residue is purified by means of FC (50 g of silica gel, dichloromethane/methanol=9:1). The title compound is obtained in the form of a diastereoisomeric mixture: R_f (dichloromethane/methanol=9:1)=0.20; R_t (I)=36.6 and 37.5 minutes; FAB-MS $(M+H)^+$=419.

The starting materials are prepared as follows:

a) N-Tert-butoxycarbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl- 8-(p-tert-butyl-phenyl)-octanoic acid (N-butyl)amide

150 m g of N-tert-butoxycarbonyl-2-methylene-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl- 8-(p-tert-butyl-phenyl)-octanoic acid (N-butyl)amide (diastereoisomer I) are hydrogenated in the presence of 150 mg of 10% Pd/C in 20 ml of tetrahydrofuran for 2 hours at room temperature and under normal pressure. The reaction mixture is filtered and concentrated by evaporation. The residue is purified by means of FC (50 g of silica gel, dichloromethane/diethyl ether= 8:2). The title compound is obtained in the form of a

diastereoisomeric mixture: R_f (dichloromethane/diethyl ether=8:2)=0.18.

b) N-Tert-butoxycarbonyl-2-methylene-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(p-tert-butyl-phenyl)-octanoic acid (N-butyl)amide

695 mg of methacrylic acid butylamide are dissolved in 30 ml of tetrahydrofuran and, at −75° C., 6.2 ml of 1.6M n-butyllithium in hexane are added thereto. The reaction mixture is stirred for 30 minutes at 0° C. and then, at −75° C., 9.8 ml of 1M chlorotitanium triisopropoxide in hexane are added thereto. The mixture is stirred for a further 15 minutes at −75° C. and then, at the same temperature, a solution of 924 mg of 2(S)-tert-butoxy-carbonyl-amino-4(S)-isopropyl-5-(p-tert-butyl-phenyl)-pentanal in 10 ml of tetrahydrofuran is added dropwise thereto. The reaction mixture is then stirred further for 15 minutes at −75° C. and for 70 minutes at 0° C. and then, in succession, 15 ml of 10% aqueous citric acid solution, water and diethyl ether are added thereto. The product is extracted repeatedly with diethyl ether. The diastereoisomeric mixture is separated by FC (700 g of silica gel, eluant: dichloromethane/diethyl ether=9:1). The title compound is obtained: diastereoisomer I: R_f (dichloromethane/diethyl ether=9:1)=0.21; diastereoisomer II:

R_f (dichloromethane/diethyl ether=9:1)=0.14.

c) 2(S)-Tert-butoxycarbonylamino-4(S)-isopropyl-5-(p-tert-butyl-phenyl)-pentanal

At −75° C., 4.2 ml of 1.2M diisobutylaluminium hydride solution in toluene are slowly added dropwise to a solution of 1 g of 2(S)-tert-butoxycarbonylamino-4(S)-isopropyl-5-(p-tert-butyl-phenyl)-pentanoic acid methyl ester in 20 ml of toluene. The reaction mixture is then stirred for a further 30 minutes at −70° C., 10 ml of methanol are added, the mixture is poured onto a mixture of ice and 10 ml of 1N hydrochloric acid, and extraction is carried out with ethyl acetate. The title compound is obtained: R_f (dichloromethane)=0.35.

d) 2(S)-Tert-butoxycarbonylamino-4(S)-isopropyl-5-(p-tert-butyl-phenyl)-pentanoic acid methyl ester

To a solution of 2.6 g of 2(S)-amino-4(S)-isopropyl-5-(p-tert-butyl-phenyl)-pentanoic acid methyl ester in 50 ml of dichloromethane there are added dropwise at 0° C. 2 ml of ethyldiisopropylamine and then a solution of 2.4 g of di-tert-butyl dicarbonate in 10 ml of dichloromethane. The reaction mixture is stirred for 16 hours at room temperature and then concentrated by evaporation. The title compound is obtained by FC (240 g of silica gel, eluant: dichloromethane): R_f (dichloromethane)=0.50.

e) 2(S)-Amino-4(S)-isopropyl-5-(p-tert-butyl-phenyl)-pentanoic acid methyl ester

With stirring at room temperature, 36 ml of 1N hydrochloric acid am added to a solution of 3.55 g of 2(R)-isopropyl-5(S)-[2(S)-isopropyl-3-(p-tert-butylphenyl)-propyl]-2,5-dihydro- 3,6-dimethoxy-pyrazine in 35 ml of acetonitrile and the mixture is then stirred for a further 3 hours. The reaction solution is then poured onto a mixture of 45 ml of saturated $NaHCO_3$ solution and ice and the suspension is extracted with dichloromethane. The extracts are concentrated by evaporation and purified by FC (700 g of silica gel, eluant: dichloromethane/methanol/NH_3=200:10:1), yielding the title compound: R_f (dichloromethane/methanol/conc. ammonia=200:10:1)=0.70.

f) 2(R)-Isopropyl-5(S)-[2(S)-isopropyl-3-(p-tert-butyl-phenyl)-propyl]-2,5-dihydro- 3,6-dimethoxypyrazine

To a solution of 2.6 ml of 2(R)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-pyrazine in 30 ml of tetrahydrofuran there are added dropwise, with stirring at −70° C., 8.2 ml of 1.6M butyl-lithium solution in hexane and, after a further 15 minutes' stirring, a solution of 2.8 g of 1-bromo-2(R)-isopropyl-3-(p-tert-butyl-phenyl)-propane in 10 ml of tetrahydrofuran. The reaction mixture is stirred further for 2 hours at −70° C. and for 3 hours at −25° C., is left to stand for 20 hours at −10° C. and is then concentrated by evaporation. Saturated ammonium chloride solution and water are added to the residue and extraction is carried out with diethyl ether. The extracts are concentrated by evarporation and purified by FC (200 g of silica gel, eluant: dichloromethyan/hexane=1:1). The title comound is obtained: R_f (dichloromethane/hexane=1:1)=0.30.

g) 1-Bromo-2(R)-isopropyl-3-(p-tert-butyl-phenyl)-propane

To a solution of 2.3 g of 2(R)-isopropyl-3-(p-tert-butyl-phenyl)-propanol in 50 ml of dichloromethane there are added, with stirring at 0° C., 3.15 g of triphenylphosphine and then, in portions, 2.14 g of N-bromosuccinimide. The reaction mixture is subsequently stirred for 16 hours at room temperature and is then concentrated by evaporation. The residue is purified by FC (100 g of silica gel, eluant; dichloromethane/hexane=1:1). The title compound is obtained: R_f (hexane)=0.49.

h) 2(R)-Isopropyl-3-(p-tert-butyl-phenyl)-propanol

With stirring at 0° C., a solution of 8.63 g of 3-[2(R)-isopropyl- 3-(p-tert-butyl-phenyl)-propanoyl]-4(R)-benzyl-oxazolidin-2-one in 40 ml of tetrahydrofuran is added dropwise to a suspension of 2.41 g of $LiAlH_4$ in 160 ml of tetrahydrofuran. The reaction mixture is stirred for a further 4 hours at 0° C. and then, at 0° C., 5 ml of ethyl acetate, 30 ml of a mixture of tetrahydrofuran/water=1:1 and then 80 ml of 2N sulfuric acid are added in succession thereto. The suspension is extracted with ethyl acetate and the extracts are concentrated by evaporation and purified by FC (700 g of silica gel, eluant: dichloromethane). The title compound is obtained: R_f (dichloromethane)=0.34; m.p.=49°–51° C.

i) 3-[2(R)-Isopropyl-3-(p-tert-butyl-phenyl)-propionyl]-4-(R)-benzyl-oxazolidin-2-one

30 ml of tetrahydrofuran are added to a solution of 31 ml of 1M lithium hexamethyl-disilazide and the mixture is stirred at −70° C. A solution of 3-isovaleroyl-4(R)-benzyloxazolidin- 2-one in 20 ml of tetrahydrofuran is then added dropwise thereto and the reaction mixture is stirred for a further 1 hour at −70° C. A solution of 9.6 g of p-tert-butylbenzyl bromide in 20 ml of tetrahydrofuran is then added dropwise thereto and the reaction mixture is stirred for a further 1 hour at −25° C. and then for 4 hours at 0° C. 6 ml of saturated ammonium chloride solution are then added to the reaction mixture, which is freed of tetrahydrofuran by means of concentration and then subjected to extraction with diethyl ether. The extract is concentrated by evaporation and the residue is purified by FC (700 g of silica gel, eluant: dichloromethane/hexane=1:1), yielding the title compound: R_f (dichloromethane/hexane=1:1)=0.30; m.p.=123.5°–124° C.

EXAMPLE 2

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-ethyl-8-(p-tert-butyl-phenyl)-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from N-tert-butoxycarbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-ethyl-8-(p-tert-butyl-phenyl)-octanoic acid (N-butyl)amide and is purified by FC (20 g of

silica gel, eluant: dichloromethane/methanol=95:5). Title compound: R_f (dichloromethane/methanol=95:5)=0.09; R_t (I)=43.31 minutes; FAB-MS $(M+H)^+$=405.

The starting material is prepared analogously to Example 1, except that in step i) instead of 3-isovaleroyl-4(R)-benzyl-oxazolidin-2-one there is used 3-butyroyl-4(R)-benzyl-oxazolidin- 2-one.

EXAMPLE 3

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-methyl-8-biphenyl-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 100 mg of N-tert-butoxycarbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-methyl-8-biphenyl-octanoic acid (N-butyl)amide and is purified by FC (50 g of silica gel, eluant: dichloromethane/methanol=9:1). This yields the pure title compound: R_f (dichloromethane/methanol=9:1)=0.11; R_t (I)=29 minutes; FAB-MS $(M+H)^+$=411.

The starting material is obtained analogously to Example 1, except that in step i) instead of 3-isovaleroyl-4(R)-benzyl-oxazolidin-2-one there is used 3-propionyl-4(R)-benzyl-oxazolidin- 2-one and instead of p-tert-butyl-benzyl bromide there is used p-phenylbenzyl bromide.

EXAMPLE 4

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-ethyl-8-(4-propyloxymethyl-naphth- 2-yl)-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 51 mg of N-tert-butoxycarbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-ethyl-8-(4-propyloxymethyl-naphth- 2-yl)-octanoic acid (N-butyl)amide and is purified by means of FC (15 g of silica gel, eluant: dichloromethane/methanol=8:2). Title compound: R_f (dichloromethane/methanol=8:2)=0.48; FAB-MS $(M+H)^+$=471.

The starting material is obtained analogously to Example 1, step i) being altered as follows:

3-[2(S)-Ethyl-3-(4-propyloxymethyl-naphth-2-yl)-propionyl]-4(R)-benzyl-oxazolidin-2-one:

30 ml of tetrahydrofuran and a solution of 2.97 g of 3-butyroyl-4(R)-benzyl-oxazolidin- 2-one in 15 ml of tetrahydrofuran are added dropwise in succession to a solution, stirred at −75° C., of 12 ml of 1M lithium hexamethyldisilazide solution. The reaction mixture is stirred for 1 hour at −75° C., a solution of 3.52 g of 4-propoxymethyl-2-bromomethyl-naphthalene in 15 ml of tetrahydrofuran is added dropwise thereto and the mixture is then stirred further for 1 hour at −30° C. and for 3 hours at 0° C. After the dropwise addition at 0° C. of 2.7 ml of saturated ammonium chloride solution, the reaction mixture is concentrated by evaporation and the residue is partitioned between diethyl ether and water. The organic extracts are concentrated by evaporation and the residue is purified by FC (1 kg of silica gel, eluant: dichloromethane/hexane=3:1), yielding the title compound: R_f (dichloromethane/hexane=3:1)=0.24; FAB-MS $(M+Na)^+$ =482.

EXAMPLE 5

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide hydrochloride

30 mg of N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide are treated with 0.6 ml of 4N hydrochloric acid in dioxane analogously to Example 1 and the product is purified by means of FC (15 g of silica gel, dichloromethane/methanol=9:1). The title compound is obtained: R_f (dichloromethane/methanol=9:1)=0.17; R_t (I)=28.54 minutes; FAB-MS $(M+H)^+$=435.

The starting materials are prepared as follows:

a) N-Tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy- 4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide

860 mg of N-tert-butoxycarbonyl-2-methylene-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl- 8-(3-benzyloxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide are hydrogenated for 3 hours at room temperature and under normal pressure in the presence of 860 mg of 50% Pd/C in 30 ml of methanol. The reaction mixture is filtered and concentrated by evaporation. The residue is purified by means of FC (100 g of silica gel, dichloromethane/ethyl acetate=9:1) with separation of the diastereoisomers. The title compound is obtained: R_f (dichloromethane/ethyl acetate=8:2)=0.23.

The unseparated diastereoisomeric mixture N-tert-butoxycarbonyl-2(R,S)-methyl-4(S)-hydroxy- 5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide has an R_f (ethyl acetate/hexane=1:1) of 0.38.

a') N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy- 4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide can also be prepared as follows:

175 mg of N-tert-butoxycarbonyl-2-methylene-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl- 8-(3-benzyloxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide are hydrogenated in the presence of 12 mg of $[Ru_2Cl_4(S\text{-}Binap)_2]$.(NEt_3) in 30 ml of methanol for 20 hours at room temperature and under 30 bar. The reaction mixture is filtered, concentrated by evaporation and purified by means of FC (hexane/ethyl acetate=1:1). The title compound so obtained (R_f in hexane/ethyl acetate=1:1)=0.15 is deprotected by hydrogenation with 90 mg of 10% Pd/C in 10 ml of methanol at room temperature and under normal pressure to form N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide.

The starting material is prepared analogously to Example 1, steps b) to g), the 2(S)-isopropyl- 3-(3-benzyloxy-4-tert-butyl-phenyl)-propanol used in step g) being prepared as follows:

h) 2(R)-Isopropyl-3-(3-benzyloxy-4-tert-butyl-phenyl)-propanol

At room temperature with stirring, to a solution of 5.65 g of 2(R)-isopropyl-3-(3-hydroxy- 4-tert-butyl-phenyl)-propanol in 100 ml of dimethylformamide there are added 11 g of caesium carbonate and, dropwise, a solution of 3.2 ml of benzyl bromide in 20 ml of dimethylformamide. The reaction mixture is stirred at room temperature for a further 16 hours and then concentrated by evaporation, and the residue is partitioned between diethyl ether and water. The organic

phases are concentrated by evaporation and the residue is purified by FC (90 g of silica gel, dichloromethane/hexane=9:1), yielding the title compound: R_f (dichloromethane/hexane=9:1)=0.44.

i) 2(R)-Isopropyl-3-(3-hydroxy-4-tert-butyl-phenyl)-propanol

To a solution, stirred at 0° C., of 12.3 ml of benzyl mercaptan in 100 ml of tetrahydrofuran there are added dropwise 49 ml of a 1.6M solution of butyllithium in hexane and after a further 15 minutes' stirring at 0° C. a solution of 12.1 g of 3-[2(R)-isopropyl-3-(3-acetoxy- 4-tert-butyl-phenyl)-propanoyl]-4(R)-benzyl-oxazolidin-2-one in 100 ml of tetrahydrofuran. The reaction solution is stirred at 0° C. for a further 90 minutes and is then added dropwise at 0° C., with stirring, to a suspension of 4.9 g of $LiAlH_4$ in 100 ml of tetrahydrofuran. The reaction mixture is stirred for a further 150 minutes at 0° C. and then, in succession, 26.8 ml of ethyl acetate, 100 ml of tetrahydrofuran/water=1:1 and 400 ml of 2N H_2SO_4 are added dropwise thereto. The tetrahydrofuran is removed using a rotary evaporator and the suspension that remains is partitioned between diethyl ether and water. The organic phases are concentrated by evaporation and the residue is purified by FC (300 g of silica gel, dichloromethane/ethyl acetate=9:1 and 200 g of silica gel, ethyl acetate/hexane=1:2), yielding the title compound: R_f (ethyl acetate/hexane=1:2)=0.43.

k) 3-[2(R)-Isopropyl-3-(3-acetoxy-4-tert-butyl-phenyl)-propanoyl]-4(R)-benzyl-oxazolidin- 2-one

Analogously to Example 1e), the title compound is obtained starting from 3-acetoxy- 4-tert-butyl-benzyl bromide and by purification using FC (silica gel, dichloromethane/hexane=7:3): R_f (dichloromethane/hexane=8:2)=0.29.

l) 3-Acetoxy-4-tert-butyl-benzyl bromide

16.4 g of N-bromosuccinimide, 1 g of α,α'-azoisobutyronitrile and 1 g of dibenzoyl peroxide are added in succession to a solution, stirred at 70° C., of 19 g of 3-acetoxy-4-tert-butyltoluene in 900 ml of CCl_4. The reaction mixture is stirred under reflux for 3½ hours under UV irradiation and is filtered, and the filtrate is concentrated by evaporation. The title compound is obtained from the residue by means of FC (900 g of silica gel, hexane/ethyl acetate=95:5): R_f (hexane/ethyl acetate=95:5)=0.40.

EXAMPLE 6

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(2-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 20 mg of N-tert-butoxycarbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(2-hydroxy- 4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide by removal of the N-tert-butyloxy-carbonyl group using 4N hydrochloric acid in dioxane, and is purified by means of FC (8 g of silica gel, dichloromethane/methanol=9:1). R_f (dichloromethane/methanol=8:2)=0.50; R_t (I) 28.47, 28.99 minutes; FAB-MS $(M+H)^+$=435.

The starting materials are prepared as follows:

a) N-Tert-butoxycarbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(2-hydroxy- 4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide

The title compound is prepared analogously to Example 5a) starting from N-tert-butoxy-carbonyl- 2-methylene-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(2-benzyloxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide and is purified by means of FC (silica gel, hexane/ethyl acetate=2:1, ethyl acetate): R_f (hexane/ethyl acetate=1:1)=0.36.

That starting material is obtained analogously to Example 5, the 2-benzyloxy-4-tert-butyl-benzyl bromide to be used in step k) being prepared as follows:

l) 2-Benzyloxy-4-tert-butyl-benzyl bromide

2.9 ml of trimethylsilyl bromide are added to a solution, stirred at room temperature, of 4 g of 2-benzyloxy-4-tert-butyl-benzyl alcohol in 100 ml of chloroform. The reaction mixture is stirred for a further 1 hour and then partitioned between trichloromethane and water. The organic phases are dried with Na_2SO_4 and concentrated by evaporation, yielding the title compound: R_f (dichloromethane/hexane=8:2)=0.95.

m) 2-Benzyloxy-4-tert-butyl-benzyl alcohol

A solution of 6.44 g of 2-benzyloxy-4-tert-butylbenzoic acid benzyl ester in 10 ml of tetrahydrofuran is slowly added dropwise to a suspension, stirred at room temperature, of 0.47 g of $LiAlH_4$ in 40 ml of tetrahydrofuran. The reaction mixture is stirred for a further 4 hours at room temperature and then, in succession, 0.96 ml of ethyl acetate, 6.4 ml of tetrahydrofuran/water=1:1 and 9.6 ml of 2N H_2SO_4 are added dropwise thereto. The suspension is partitioned between ethyl acetate and water/saturated sodium chloride solution, the organic phases are concentrated by evaporation and the residue is purified by means of FC (150 g of silica gel, dichloromethane/hexane=6:4). Title compound: R_f (dichloromethane/hexane=8:2)=0.24.

n) 2-Benzyloxy-4-tert-butyl-benzoic acid benzyl ester

A mixture of 5 g of 2-hydroxy-4-tert-butyl-benzoic acid, 9.1 ml of benzyl bromide, 17 g of caesium carbonate, 0.3 g of sodium iodide and 500 ml of acetone is stirred for 20 hours under reflux and then filtered and the filtrate is concentrated by evaporation. The residue is partitioned between diethyl ether and water, the organic phases are concentrated by evaporation and the residue is purified by means of FC (1000 g of silica gel, dichloromethane/hexane=1:1). Title compound: R_f (dichloromethane/hexane=1:1)=0.47.

EXAMPLE 7

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-ethoxycarbonylmethoxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 62 mg of N-tert-butoxy-carbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-ethoxycarbonylmethoxy- 4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide and is purified by means of FC (20 g of silica gel, dichloromethane/methanol=9:1). This yields the title compound: R_f (dichloromethane/methanol=9:1)=0.33; R_t (I)= 34.5 and 34.8 minutes; FAB-MS $(M+H)^+$=521.

The starting materials are obtained as follows:

a) N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-ethoxycarbonyl-methoxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide

A mixture of 52 mg of N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino- 7(S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide (Example 5a), 47.5 mg of caesium carbonate, 0.012 ml of iodoacetic acid ethyl ester and 5 ml of acetone is stirred for

3 hours under reflux and then concentrated by evaporation. The residue is partitioned between diethyl ether and water. The organic phases are dried and combined and then concentrated by evaporation, yielding the title compound in the form of the crude product: R_f (dichloromethane/diethyl ether=8:2)=0.28.

EXAMPLE 8

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-allyloxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 45 mg of N-tert-butoxy-carbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-allyloxy- 4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide and is purified by FC (20 g of silica gel, dichloromethane/methanol=9:1). This yields the title compound: R_f (dichloromethane/methanol=9:1)=0.20; FAB-MS $(M+H)^+$=475.

The starting material is prepared analogously to Example 7a) using allyl iodide.

EXAMPLE 9

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-methoxycarbonylallyloxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 100 mg of N-tert-butoxy-carbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-methoxycarbonylallyloxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide. This yields the title compound in the form of a diastereoisomeric mixture: R_f (dichloromethane/methanol=9:1)=0.36; R_t (I)=25.32 and 25.8 minutes; FAB-MS $(M+H)^+$=533.

The starting material is prepared analogously to Example 7a) using N-tert-butoxycarbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide and 4-bromo-2-butenoic acid methyl ester.

EXAMPLE 10

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-methoxy-carbonylmethoxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 91 mg of N-tert-butoxy-carbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-methoxy-carbonylmethoxy- 4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide and is purified by FC (15 g of silica gel, ethyl acetate/methanol=8:2). This yields the title compound in the form of a diastereoisomeric mixture: R_f (ethyl acetate/methanol=8:2)=0.45; R_t (I)=32.5 and 33.0 minutes; FAB-MS $(M+H)^+$=507.

The starting material is prepared analogously to Example 7a) using N-tert-butoxy-carbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide and bromoacetic acid methyl ester.

EXAMPLE 11

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-carbamoyl-methoxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide

Analogously to Example 1, the title compound is prepared starting from 59 mg of N-tert-butoxy-carbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-carboxamidomethoxy- 4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide and is purified by FC (20 g of silica gel, dichloromethane/methanol/conc. ammonia=140:10:1). This yields the title compound in the form of a diastereoisomeric mixture: R_f (dichloromethane/methanol/conc. ammonia=140:10:1)=0.23 and 0.32; R_t (I)=25.08 and 25.59 minutes; FAB-MS $(M+H)^+$=492.

The starting material is prepared analogously to Example 7a) using N-tert-butoxy-carbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide and iodoacetamide.

EXAMPLE 12

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-3-(pyrid-2-yl, methoxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 40 mg of N-tert-butoxy-carbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(pyrid- 2-ylmethoxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound in the form of a diastereoisomeric mixture: R_f (dichloromethane/methanol=9:1)=0.32; R_t (I)=24.52 and 25.19 minutes; FAB-MS $(M+H)^+$=526.

The starting material is prepared analogously to Example 7a) using N-tert-butoxy-carbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide and 2-picolyl chloride hydrochloride.

EXAMPLE 13

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(pyrid-4-yl-methoxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 46 mg of N-tert-butoxy-carbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(pyrid-4-yl-methoxy)- 4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound in the form of a diastereoisomeric mixture: R_f (dichloromethane/methanol=9:1)=0.17; R_t (I)=20.27 and 20.62 minutes; FAB-MS $(M+H)^+$=526.

The starting material is prepared analogously to Example 7a) using N-tert-butoxy-carbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide and 4-picolyl chloride hydrochloride.

EXAMPLE 14

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(N-oxido-pyrid-2-yl-methoxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 35 mg of N-tert-butoxy-carbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(N-oxidopyrid-2-yl-methoxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound in the form of a diastereoisomeric mixture: R_f (dichloromethane/methanol =9:1)=0.14; R_t (I)=31.06 and 31.6 minutes; FAB-MS $(M+H)^+$=542.

The starting material is prepared analogously to Example 7a) using N-tert-butoxy-carbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-octanoic acid N-(butyl)amide and 2-picolyl chloride N-oxide.

EXAMPLE 15

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2-ethoxycarbonylallyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 30 mg of N-tert-butoxy-carbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2-ethoxycarbonylallyloxy)- 4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound in the form of a diastereoisomeric mixture: R_f (dichloromethane/methanol=9:1)=0.28; R_t (I)=39.3 and 39.8 minutes FAB-MS $(M+H)^+$=547.

The starting material is prepared analogously to Example 7a) using N-tert-butoxycarbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide and bromomethylacrylic acid ethyl ester.

EXAMPLE 16

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2-ethoxycarbonylpropyloxy)-4-tert-butyl-phenyl-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 9 mg of N-tert-butoxy-carbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2-ethoxycarbonyl-propyloxy)- 4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound in the form of a diastereoisomeric mixture: R_f (dichloromethane/methanol =9:1)=0.25; R_t (I)=38.5; 39.0; 39.6 and 40.2 minutes; FAB-MS $(M+H)^+$=549.

The starting material is prepared by hydrogenating N-tert-butoxycarbonyl-2(R,S)-methyl- 4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2-ethoxycarbonylallyloxy)- 4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide (Example 15) with Raney nickel in ethanol at room temperature and under 2 bar H_2: R_f (ethyl acetate/hexane=1:2)=0.16.

EXAMPLE 17

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(methylthio-methoxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 10 mg of N-tert-butoxycarbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(methylthio-methoxy)- 4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound in the form of a diastereoisomeric mixture: R_f (dichloromethane/methanol= 9:1)=0.2; R_t (I)=29.32 and 29.56 minutes; FAB-MS $(M+H)^+$ =495.

The starting material is prepared as follows:

a) N-Tert-butoxycarbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(methylthio-methoxy)- 4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide

A solution of 100 mg of N-tert-butoxycarbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino- 7(S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide (Example 5a) in 5 ml of dimethylformamide is added dropwise to a suspension, stirred at room temperature, of 7.6 mg of a 65% NaH dispersion in 3 ml of dimethylformamide. The reaction mixture is stirred for a further 30 minutes at room temperature and then a solution of 0.017 ml of chlorodimethyl sulfide in 2 ml of dimethylformamide is added thereto. The reaction mixture is stirred for a further 24 hours and then concentrated by evaporation. The residue is partitioned between ether and water. The organic phases are concentrated by evaporation and the title compound is obtained from the residue by FC (12 g of silica gel, dichloromethane/diethyl ether=2:1): R_f (dichloromethane/diethyl ether=2:1)=0.33.

EXAMPLE 18

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7-(S)-isopropyl-8-[3-(methyl-sulfonyl-methoxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 15 mg of N-tert-butoxy-carbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(methyl-sulfonyl-methoxy)- 4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound in the form of a diastereoisomeric mixture: R_f (dichloromethane/methanol=9:1)=0.75; R_t (I)=28.3 and 28.76 minutes; FAB-MS $(M+H)^+$=527.

The starting material is prepared as follows:

a) N-Tert-butoxycarbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(methylsulfonyl-methoxy)- 4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide

With stirring at 0° C., a solution of 115 mg of potassium monopersulfate triple salt in 0.5 ml of water is added dropwise to a solution of 74 mg of N-tert-butoxycarbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(methylthio-methoxy)- 4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide in 0.5 ml of methanol and the mixture is then stirred at room temperature for a further 20 hours. The reaction mixture is partitioned between dichloromethane and water. The organic phases are concentrated by evaporation and the title compound is obtained from the

residue by FC (11 g of silica gel, ethyl acetate/hexane=1:1): R_f (ethyl acetate/hexane=1:1)=0.26; FAB-MS $(M+H)^+$=627.

EXAMPLE 19

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(carboxy-methoxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 28 mg of N-tert-butoxy-carbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(carboxy-methoxy)- 4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound in the form of a diastereoisomeric mixture: R_f (dichloromethane/methanol=9:1)=0.26; R_t (I)=26.1 and 28.0 minutes; FAB-MS $(M+H)^+$=493.

The starting material is prepared analogously to Example 7a) using N-tert-butoxy-carbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-butyl-phenyl)-octanoic acid (N-butyl)amide and bromoacetic acid benzyl ester, with subsequent removal of the benzyl group by hydrolysis (Pd/C-ethanol).

EXAMPLE 20

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3,3-dimethyl-2-oxo-butyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 42 mg of N-tert-butoxy-carbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3,3-dimethyl- 2-oxo-butyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound in the form of a diastereoisomeric mixture: R_f (dichloromethane/methanol=9:1)=0.3; R_t (I)=37.3 and 37.8 minutes; FAB-MS$(M+H)^+$=533.

The starting material is prepared analogously to Example 17a) using N-tert-butoxy-carbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy- 4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide and 1-bromopinacolone.

EXAMPLE 21

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2-nitrobenzyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 53 mg of N-tert-butoxy-carbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2-nitrobenzyloxy)- 4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound in the form of a diastereoisomeric mixture: R_f (dichloromethane/methanol=9:1)=0.35; R_t (I)=52.0 and 52.4 minutes; FAB-MS$(M+H)^+$=570.

The starting material is prepared analogously to Example 7a) using N-tert-butoxy-carbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-butyl-phenyl)-octanoic acid (N-butyl)amide and 2-nitrobenzyl chloride.

EXAMPLE 22

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2-amino-benzyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide hydrochloride

The title compound is prepared starting from 35 mg of 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino- 7(S)-isopropyl-8-[3-(2-nitrobenzyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide (Example 21) by hydrogenation with Pt/C in tetrahydrofuran at room temperature and under normal pressure and is purified by FC (10 g of silica gel, dichloromethane/methanol=9:1). This yields the title compound in the form of a diastereoisomeric mixture: R_f (dichloromethane/methanol=9:1)=0.27; R_t (I)=30.5 and 31.3 minutes; FAB-MS$(M+H)^+$=539.

EXAMPLE 23

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-chloro-2(R,S)-hydroxy-propyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 31 mg of N-tert-butoxy-carbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2,3-epoxypropyloxy)- 4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound in the form of a diastereoisomeric mixture: R_f (dichloromethane/methanol=9:1)=0.18; R_t (I)=31.9 and 32.3 minutes; FAB-MS$(M+H)^+$=527.

The starting material is prepared analogously to Example 7a) using N-tert-butoxy-carbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy- 4-tert-butylphenyl)-octanoic acid (N-butyl)amide and epibromohydrin.

EXAMPLE 24

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-methylthio-2(S,R)-hydroxypropyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 15 mg of N-tert-butoxy-carbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-methylthio- 2(S,R)-hydroxypropyloxy)-4-tert-butyl-phenyl] -octanoic acid (N-butyl)amide. This yields the title compound in the form of a diastereoisomeric mixture: R_f (dichloromethane/methanol=9:1)=0.32; R_t (I)=32.6 and 32.9 minutes; FAB-MS$(M+H)^+$=53

The starting material is prepared as follows:

a) N-tert-butoxycarbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-methylthio-2(S,R)-hydroxypropyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide

18 mg of sodium methanethiolate are added to a solution of 150 mg of N-tert-butoxycarbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2,3-epoxypropyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide in 10 ml of methanol and the mixture is maintained under reflux for 7 hours. The reaction mixture is concentrated by evaporation and the residue is partitioned between dichloromethane and water. The organic phases are concentrated by evaporation and the title compound is obtained from the

residue after purification by means of FC (20 g of silica gel, dichloromethane/diethyl ether=1:1): R_f (dichloromethane/diethyl ether=1:1)=0.33; FAB-MS $(M+H)^+$=639.

EXAMPLE 25

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-methylsulfonyl-2(S,R)-hydroxypropyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 14 mg of N-tert-butoxy-carbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-methyl-sulfonyl- 2(S,R)-hydroxypropyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound in the form of a diastereoisomeric mixture: R_f (dichloromethane/methanol=9:1)=0.16; R_t (I)=26.3 and 26.8 minutes; FAB-MS$(M+H)^+$=571.

The starting material is prepared analogously to Example 18a) using 62 mg of N-tert-butoxycarbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-methylthio- 2(S,R)-hydroxypropyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide: R_f (ethyl acetate)=0.60; FAB-MS $(M+H)^+$=671.

EXAMPLE 26

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(methylsulfonyl-methoxy)-4-tert-butyl-phenyl]-octanoic acid (N-3-morpholino-propyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 18 mg of N-tert-butoxy-carbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-methyl-sulfonyl-methoxy)- 4-tert-butyl-phenyl)-octanoic acid (N-3-morpholino-propyl)amide. This yields the title compound: R_f (dichloromethane/methanol=8:2)=0.16; R_t (I)=17.61 minutes; FAB-MS$(M+H)^+$=598.

The starting material is prepared analogously to Examples 17a) and 18a) using N-tert-butoxycarbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)octanoic acid (N-3-morpholino-propyl)amide and chlorodimethyl sulfide.

The N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy- 4-tert-butyl-phenyl)-octanoic acid (N-3-morpholino-propyl)amide is prepared analogously to Example 5a-1), except that in step 5b) or 1b) methacrylic acid (N-3-morpholino-propyl)amide is used instead of methacrylic acid butylamide.

EXAMPLE 27

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-methoxycarbonylmethoxy-phenyl)-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 12 mg of N-tert-butoxy-carbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-methoxycarbonyl-methoxy-phenyl)-octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol=9:1)=0.18; R_t (I)=21.74 minutes; FAB-MS$(M+H)^+$=451.

The starting material is prepared analogously to Example 7a) using N-tert-butoxy-carbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxyphenyl)-octanoic acid (N-butyl)amide and bromoacetic acid methyl ester.

The N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxyphenyl)-octanoic acid (N-butyl)amide used as starting material is prepared analogously to Example 5a)-5l), except that in step k) instead of 3-acetoxy-4-tert-butyl-benzyl bromide there is used 3-benzyloxy-benzyl bromide, so that in step i) 2(R)-isopropyl- 3-(3-benzyloxy-phenyl)-propanol, R_f (dichloromethane/hexane=1:1)=0.19, is obtained directly.

EXAMPLE 28

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(methoxycarbonylmethoxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 15 mg of N-tert-butoxy-carbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(methoxy-carbonylmethoxy)- 4-methoxy-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol=9:1)=0.16; R_t (I)=19.33 minutes; FAB-MS$(M+H)^+$= 481.

The starting material is prepared analogously to Example 7a) using N-tert-butoxy-carbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide and bromoacetic acid methyl ester.

The N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy- 4-methoxy-phenyl)-octanoic acid (N-butyl)amide used as starting material is prepared as follows:

a1) N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-benzyloxy- 4-methoxy-phenyl)-octanoic acid (N-butyl)amide

3.5 g of N-tert-butoxycarbonyl-2-methylene-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-benzyloxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide are hydrogenated in 30 ml of absolute methanol in the presence of 20 mg of $[Ru_2Cl_4((S)\text{-Binap})_2].NEt_3$ at room temperature and 25 bar for 5 hours. The reaction mixture is filtered and the filtrate is concentrated by evaporation. The residue is purified by FC (200 g of silica gel, hexane/ethyl acetate=1:1). Title compound: R_f (hexane/ethyl acetate=1:1)=0.16; FAB-MS $(M+H)^+$= 599.

a2) N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy- 4-methoxy-phenyl)-octanoic acid (N-butyl)amide

4.7 g of N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-benzyloxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide are hydrogenated in 60 ml of methanol in the presence of 2.35 g of 10% Pd/C at room temperature and under normal pressure for 1 hour. Filtration of the reaction mixture and concentration of the filtrate by evaporation under a high vacuum yield the title compound: R_f (hexane/ethyl acetate =1:1)=0.15; FAB-MS $(M+H)^+$= 509.

The N-tert-butoxycarbonyl-2-methylene-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-benzyloxy- 4-methoxy-phenyl)-octanoic acid (N-butyl)amide used as starting material is prepared analogously to Example 1 b) to i), except that in step i) 3-benzyloxy-4-methoxy-benzyl bromide is used instead of p-tert-butyl benzyl bromide.

EXAMPLE 29

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(N-methylcarbamoylmethoxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 18 mg of N-tert-butoxy-carbonyl- 2(R)-methoxy-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(N-methyl-carbamoylmethoxy)- 4-methoxy-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol=9:1)=0.21; R_t (I)=15.54 minutes; FAB-MS(M+H)$^+$=480.

The starting material is prepared as follows:

A mixture of 29 mg of N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino- 7(S)-isopropyl-8-[3-(methoxycarbonylmethoxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide (Example 32), 6 ml of dimethylformamide and 1 ml of methylamine is left to stand in a bomb tube at room temperature for 60 hours. Concentration by evaporation and FC (5 g of silica gel, dichloromethane/methanol=9:1) of the residue yield the title compound: R_f (dichloromethane/methanol=9:1)=0.55.

EXAMPLE 30

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-methyl-sulfonyl-propyloxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 30 mg of N-tert-butoxy-carbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-methylsulfonyl-propyloxy)- 4-methoxy-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol=9:1)=0.29; R_t (I)=17.83 minutes; FAB-MS(M+H)$^+$=529.

The starting material is prepared analogously to Examples 17a) and 18a) using N-tert-butoxycarbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-methoxy-phenyl)-octanoic acid (N-butyl)amide and 3-methylthiopropyl iodide with subsequent oxidation to the sulfone.

EXAMPLE 31

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(methylsulfonyl-methoxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 100 mg of N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(methylsulfonyl-methoxy)- 4-methoxy-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol=8:2)=0.5; R_t (I)=18.0 minutes; FAB-MS(M+H)$^+$=501.

The starting material is prepared analogously to Examples 17a) and 18a) using N-tert-butoxycarbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide and chlorodimethyl sulfide with subsequent oxidation to the sulfone.

EXAMPLE 32

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-methoxy-propyloxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 27 mg of N-tert-butoxy-carbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-methoxy-propyloxy)- 4-methoxy-phenyl]-octanoic acid (N-butyl)amide and is purified by FC (2 g of silica gel, dichloromethane/methanol=95:5). This yields the title compound: R_f (dichloromethane-methanol=9:1)=0.15; R_t (I)= 21.9 minutes; FAB-MS(M+H)$^+$=481.

The starting material is prepared analogously to Example 17a) using N-tert-butoxy-carbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide and 3-methoxypropyl iodide.

EXAMPLE 33

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2-methoxyethoxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 68 mg of N-tert-butoxy-carbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2-methoxyethoxy)- 4-methoxy-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol=9:1)=0.32; R_t (I)=19.84 minutes; FAB-MS(M+H)$^+$=467.

The starting material is prepared analogously to Example 17a) using N-tert-butoxy-carbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide and 2-methoxyethyl iodide.

EXAMPLE 34

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-hydroxy-propyloxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 93 mg of N-tert-butoxy-carbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-hydroxy-propyloxy)- 4-methoxy-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol=9: 1)=0.24; R_t (I)=16.13 minutes; FAB-MS(M+H)$^+$=467.

The starting material is prepared analogously to Example 17a) using N-tert-butoxy-carbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide and 3-iodopropanol.

EXAMPLE 35

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(carbamoyl-methoxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 39 mg of N-tert-butoxy-carbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(car-

bamoyl-methoxy)- 4-methoxy-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol=8:2)=0.38; R_t (I)=13.86 minutes; FAB-MS(M+H)$^+$=466.

The starting material is prepared analogously to Example 7a) using N-tert-butoxy-carbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide and iodoacetamide.

EXAMPLE 36

2(R)-Methyl-4(S)-hydroxy-5-(S)-amino-7(S)-isopropyl-8-(3-cyanomethoxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide

1.5 ml of a mixture of trifluoroacetic acid/dichloromethane=1:3 are added at 0° C., with stirring, to a solution of 35 mg of N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino- 7(S)-isopropyl-8-(3-cyanomethoxy-4-methoxy-phenyl)-octanoic acid (N-butyl)-amide in 1 ml of dichloromethane, and the mixture is stirred for a further 3 hours at 0° C. and then concentrated by evaporation. The residue is purified by FC (5 g of silica gel, dichloromethane/methanol=9:1). This yields the title compound: R_f (dichloromethane/methanol=9:1)=0.19; R_t (I)=19.59 minutes; FAB-MS(M+H)$^+$=448.

The starting material is prepared analogously to Example 7a) using N-tert-butoxycarbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide and iodoacetonitrile.

EXAMPLE 37

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(4-methoxybutoxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 24 mg of N-tert-butoxy-carbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(4-methoxy-butoxy)- 4-methoxy-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol=9:1)=0.29; R_t (I)=22.51 minutes; FAB-MS(M+H)$^+$= 495.

The starting material is prepared analogously to Example 17a) using N-tert-butoxy-carbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide and 4-methoxypropyl iodide.

EXAMPLE 38

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2-ethoxy-ethoxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 24 mg of N-tert-butoxy-carbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2-ethoxy-ethoxy)- 4-methoxy-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol=9:1)=0.26; R_t (I)=21.32 minutes; FAB-MS(M+H)$^+$=481..

The starting material is prepared analogously to Example 17a) using N-tert-butoxy-carbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy- 4-methoxy-phenyl)-octanoic acid (N-butyl)amide and 2-iododiethyl ether.

EXAMPLE 39

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-{3-[2-(2-methoxy-ethoxy)ethoxy]-4-methoxy-phenyl}-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 27 mg of N-tert-butoxy-carbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-{ 3-[2-(2-methoxy-ethoxy)ethoxy]-4-methoxy-phenyl}-octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol=1:1)=0.19; R_t (I)=18.93 minutes; FAB-MS(M+H)$^+$=511.

The starting material is prepared analogously to Example 17a) using N-tert-butoxy-carbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide and 1-iodo-2-(2-methoxy-ethoxy)-ethane.

EXAMPLE 40

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-pentyloxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 53 mg of N-tert-butoxy-carbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-pentyloxy- 4-methoxy-phenyl)-octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol=9:1)=0.25; R_t (I)=32.01 minutes; FAB-MS(M+H)$^+$= 479.

The starting material is prepared analogously to Example 17a) using N-tert-butoxycarbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide and iodopentane.

EXAMPLE 41

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-benzyloxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 100 mg of N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-benzyloxy- 4-methoxy-phenyl)-octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol=9:1)=0.31; R_t (I)=44.21 minutes; FAB-MS(M+H)$^+$= 499.

The starting material is prepared analogously to Example 17a) using N-tert-butoxy-carbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide and benzyl bromide.

EXAMPLE 42

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-ethoxy-propyloxy)-4-methoxy-phenyl-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 113 mg of N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-ethoxypropyloxy)- 4-methoxy-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol=9:1)=0.30; R_t (I)=23.11 minutes; FAB-MS(M+H)$^+$=495.

The starting material is prepared analogously to Example 7a) using N-tert-butoxy-carbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide and 1-ethoxy-3-iodopropane.

EXAMPLE 43

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(pyrid-4-yl-methoxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 71 mg of N-tert-butoxycarbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(pyrid-4-yl-methoxy)- 4-methoxy-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol=9:1)=0.19; R_t (I)=32.95 minutes; FAB-MS (M+H)$^+$=500.

The starting material is prepared analogously to Example 7a) using N-tert-butoxy-carbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide and 4-picolyl chloride.

EXAMPLE 44

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(2-ethoxy-carbonylmethoxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 67 mg of N-tert-butoxy-carbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(2-ethoxy-carbonylmethoxy- 4-tert-butyl-phenyl)-octanoic acid (N-butyl)-amide. This yields the title compound in the form of a diastereoisomeric mixture: R_f (dichloromethane/methanol=9:1)=0.19; R_t (I)=35.7 and 36.5 minutes; FAB-MS(M+H)$^+$=521.

The starting material is prepared analogously to Example 7a) using N-tert-butoxy-carbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(2-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide (Example 6a) and iodoacetic acid ethyl ester.

EXAMPLE 45

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(2-ethoxy-carbonyl-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 80 mg of N-tert-butoxy-carbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(2-ethoxy-carbonylmethoxy- 4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide. This yields the title compound in the form of a diastereoisomeric mixture: R_f (dichloromethane/methanol=9:1)=0.21; R_t (I)=27.8 and 28.39 minutes; FAB-MS(M+H)$^+$=492.

The starting material is prepared analogously to Example 7a) using N-tert-butoxy-carbonyl- 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(2-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide (Example 6a) and iodoacetamide.

EXAMPLE 46

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-methoxy-propyloxy)-4,5-ethylenedioxy-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 34 mg of N-tert-butoxycarbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-methoxy-propyloxy)- 4,5-ethylenedioxy-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol=9:1)=0.16; R_t (I)=21.83 minutes; FAB-MS (M+H)$^+$=509.

The starting material is prepared analogously to Example 17a) using N-tert-butoxy-carbonyl- 2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4,5-ethylenedioxy-phenyl)-octanoic acid (N-butyl)amide and 3-methoxy-propyl iodide.

The N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy- 4,5-ethylenedioxy-phenyl)-octanoic acid (N-butyl)amide is prepared analogously to Example 28, except that in step i) instead of 3-benzyloxy-4-methoxy-benzyl bromide there is used 3-benzyloxy-4,5-ethylenedioxy-benzyl bromide. That compound is prepared as follows:

a) 5-Hydroxy-1,4-benzodioxane-7-carboxylic acid ethyl ester

A solution of 0.2 ml of 1,2-dibromoethane in 4 ml of dimethylformamide is added dropwise, four times at 2 hour intervals, to a solution, stirred at 100° C., of 2 g of gallic acid ethyl ester and 6.5 g of caesium carbonate in 80 ml of dimethylformamide. After being stirred for a further 2 hours at 100° C. the reaction mixture is concentrated by evaporation and the residue is partitioned between diethyl ether and water. The organic phases are dried over sodium sulfate and concentrated by evaporation. The title compound is obtained from the residue by FC (50 g of silica gel, methylene chloride-methanol=8:2): R_f (methylene chloride/methanol=8:2)=0.39.

b) 5-Benzyloxy-1,4-benzodioxane-7-carboxylic acid ethyl ester

The reaction mixture containing 900 ml of acetone, 17.4 g of hydroxy-1,4-benzodioxane- 7-carboxylic acid ethyl ester, 37.9 g of cacsium carbonate, 11 ml of benzyl bromide and 7.7 g of sodium iodide is stirred under reflux for 3 hours and then concentrated by evaporation. The residue is partitioned between diethyl ether and water. The organic phases are dried over sodium sulfate and concentrated by evaporation. The title compound is obtained from the residue by FC (900 g of silica gel, hexane/ethyl acetate=1:1): R_f (hexane/ethyl acetate=2:1)=0.36.

c) 5-Benzyloxy-7-hydroxymethyl-1,4-benzodioxane

A solution of 1.28 g of 5-benzyloxy-1,4-benzodioxane-7-carboxylic acid ethyl ester in 5 ml of tetrahydrofuran is

added dropwise at room temperature to a solution of 110 mg of lithium aluminium hydride in 10 ml of tetrahydrofuran and the mixture is stirred at room temperature for a further 30 minutes. Then 0.22 ml of ethyl acetate, 1.5 ml of a mixture (water/tetrahydrofuran=1:1) and finally 2.25 ml of 2N sulfuric acid are added dropwise in succession. The reaction mixture is partitioned between diethyl ether and water. The organic phases are dried over sodium sulfate and concentrated by evaporation. The title compound is obtained from the residue by FC (240 g of silica gel, ethyl acetate/hexane=1:2): R_f (ethyl acetate-hexane=1:2)=0.18.

d) 3-Benzyloxy-4,5-ethylenedioxy-benzyl bromide

0.07 ml of trimethylsilyl bromide is added to a solution of 0.1 g of 5-benzyloxy-7-hydroxymethyl- 1,4-benzodioxane in 5 ml of chloroform and the mixture is stirred for a further 15 minutes at room temperature and then concentrated by evaporation in a rotary evaporator. The residue is immediately dissolved in a small amount of ethyl acetate; the same volume of hexane is added and the mixture is filtered through 15 g of silica gel, followed by elution with a mixture (hexane/ethyl acetate=4:1). Concentration of the eluates by evaporation yields the title compound: R_f (hexane/ethyl acetate=3:1)=0.48.

EXAMPLE 47

In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-(3-hydroxy-propyloxy)- 3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-2,2-dimethyl-ethyl)]-amide hydrochloride.

EXAMPLE 48

In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-isopropyl-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-2,2-dimethyl-ethyl)]-amide hydrochloride.

EXAMPLE 49

In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-tert-butyl- 3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-2,2-dimethyl-ethyl)]amide hydrochloride.

EXAMPLE 50

In a manner analogous to that described in Examples 1 to 46 or 62 to 180, it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-(3-methyl-sulfonyl-propyloxy)- 3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-2-morpholinoethyl)amide dihydrochloride.

EXAMPLE 51

In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-(3-methyl-sulfonyl-propyloxy)- 3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl- 2,2-dimethyl-ethyl)]-amide hydrochloride.

EXAMPLE 52

In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[3,4-di(3-hydroxypropyloxy)phenyl]-octanoic acid (N-2-morpholinoethyl)amide dihydrochloride.

EXAMPLE 53

In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[3,4-di(3-hydroxypropyloxy)phenyl]-octanoic acid [N-(2-carbamoyl-2,2-dimethyl-ethyl)]-amide hydrochloride.

EXAMPLE 54

In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-(3-N-methylcarbamoyl-propyl)- 3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-2-morpholinoethyl)amide dihydrochloride.

EXAMPLE 55

In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-(2-morpholinoethoxy)- 3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl- 2,2-dimethyl-ethyl)]-amide dihydrochloride.

EXAMPLE 56

In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[3-(3-methoxy-propyloxy)- 4,5-ethylenedioxy-phenyl]-octanoic acid (N-2-morpholinoethyl)amide dihydrochloride.

EXAMPLE 57

In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[3-(3-methoxy-propyloxy)- 4,5-ethylenedioxy-phenyl]-octanoic acid [N-(2-carbamoyl-2,2-dimethyl-ethyl)]-amide hydrochloride.

EXAMPLE 58

In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[3-(3-methoxy-propyloxy)-4,5-methylenedioxy-phenyl]-octanoic acid (N-2-morpholinoethyl)amide dihydrochloride.

EXAMPLE 59

In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[3-(3-methoxy-propyloxy)- 4,5-methylenedioxy-phenyl]-octanoic acid [N-(2-carbamoyl-2,2-dimethylethyl)]-amide hydrochloride.

EXAMPLE 60

In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-car-

bamoyl-2,2-ethylene-ethyl)]-amide hydrochloride.

EXAMPLE 61

In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(3(S)-2-oxo-pyrrolidin-3-yl-methyl)]amide hydrochloride.

EXAMPLE 62

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(4-methoxy-but-2-enoxy)-phenyl]-octanoic acid (N-butyl)-amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 66 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(4-methoxy-but-2-enoxy)-phenyl]-octanoic acid (N-butyl)-amide and is purified by FC (30 g of silica gel, dichloromethane/methanol=9:1). This yields the title compound: Rf (dichloromethane/methanol=9:1)=0.26; HPLC R_t(I)= 40.4 minutes; FAB-MS $(M+H)^+$=493.

The starting material is prepared analogously to Example 17a) using 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic acid (N-butyl)-amide (Example 28) and 4-methoxy-but-2-enyl iodide.

EXAMPLE 63

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-hydroxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 20 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-hydroxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)-amide. This yields the title compound: R_f (dichloromethane/methanol=9:1)=0.05; HPLC R_t(I)=36.22 minutes; FAB-MS $(M+H)^+$=467.

The starting material is prepared as follows:

a) 5(S)-Tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-hydroxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)-amide

1.34 g of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-benzyloxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)-amide are hydrogenated in the presence of 400 mg of 5% Pd/C in 50 ml of methanol for 10 minutes at room temperature and under normal pressure. The reaction mixture is filtered and concentrated by evaporation. The residue is purified by means of FC (50 g of silica gel, hexane/ethyl acetate=1:1). The title compound is obtained: R_f (hexane/ethyl acetate= 1:1)=0.16; HPLC R_t=17.42 minutes; FAB-MS: $(M+H)^+$= 567.

The 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-benzyloxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)-amide used as starting material is prepared analogously to Example 28a1) and Examples 1b) to 1g), except that in step g) instead of 2(S)-isopropyl-3-(p-tert-butyl-phenyl)-propanol there is used 2(S)-isopropyl-3-[4-benzyloxy-3-(3-methoxypropyloxy)-phenyl]-propanol. That compound is prepared analogously to Example 124i) to m), except that in step m) instead of 4-methoxy-3-(3-methoxypropyloxy)-benzyl alcohol there is used 4-benzyloxy-3-(3-methoxypropyloxy)-benzyl alcohol.

That compound is prepared as follows:

b) 4-Benzyloxy-3-(3-methoxypropyloxy)-benzaldehyde

A solution of 28.8 g of 4-benzyloxy-3-hydroxy-benzaldehyde in 100 ml of dimethyl-formamide is added dropwise to a suspension of 5.54 g of NaH (60% dispersion in mineral oil) in 150 ml of absolute dimethylformamide. The reaction mixture is stirred at room temperature. After 30 minutes, a solution of 29 g of 3-methoxybromopropane in 120 ml of dimethylformamide is added thereto, and the mixture is stirred at room temperature for a further 4 hours and is then concentrated by evaporation under reduced pressure. The residue is partitioned between diethyl ether and water. The combined organic phases are dried over sodium sulfate and concentrated by evaporation, and the residue is purified by FC (100 g of silica gel, dichloromethane), yielding the title compound, which crystallises spontaneously: R_f (dichloromethane/diethyl ether)=0.44.

c) 4-Benzyloxy-3-(3-methoxypropyloxy)-benzyl alcohol

A solution of 31 g of 4-benzyloxy-3-(3-methoxypropyloxy)-benzaldehyde in 530 ml of ethanol/water=8:2 is added dropwise to a suspension, stirred at 0° C., of 11.74 g of sodium boranate in 530 ml of a mixture of ethanol/water= 8:2. The reaction mixture is stirred for one hour at 0° C. and is then concentrated by evaporation. The residue is partitioned between diethyl ether and water. The combined organic phases are dried over sodium sulfate and concentrated by evaporation, and the residue is purified by FC (100 g of silica gel, dichloromethane/diethyl ether=1:1), yielding the title compound: R_f (dichloromethane/diethyl ether=1:1)= 0.43.

EXAMPLE 64

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-benzyloxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 60 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-benzyloxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol=95:5)=0.08; HPLC R_t(I)=45.47 minutes; FAB-MS $(M+H)^+$=557.

EXAMPLE 65

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[3,4-di(3-methoxypropyloxy)phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 66 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[3,4-di(3-methoxypropyloxy)phenyl]-octanoic acid (N-butyl)amide. This yields the title compound: Rf (dichloromethane/methanol=9:1)=0.21; R_t(I)=40.0 minutes; FAB-MS $(M+H)^+$=539.

The starting material is prepared analogously to Example 17a) using 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-hydroxy-3-(3-methoxy-

propyloxy)-phenyl]-octanoic acid (N-butyl)amide and 3-methoxy-bromopropane.

EXAMPLE 66

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(2,2,2-trifluoroethoxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic. acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 14 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(2,2,2-trifluoro-ethoxy)- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol=9:1)=0.31; HPLC R_t(I)=28.7 minutes; FAB-MS $(M+H)^+$=549.

The starting material is prepared analogously to Example 17a) using 5(S)-tert-butoxy-carbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-hydroxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)amide and 2,2,2-trifluoroethyl iodide.

EXAMPLE 67

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(3-hydroxypropyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 20 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(3-hydroxy-propyloxy)- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide and is purified by FC (2 g of silica gel, dichloromethane/methanol=9:1). This yields the title compound: R_f (dichloromethane/methanol=9:1)=0.09; HPLC R_t=11.03 minutes; FAB-MS $(M+H)^+$=525.

The starting material is prepared analogously to Example 17a) using 5(S)-tert-butoxy-carbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-hydroxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)amide and 3-iodopropanol.

EXAMPLE 68

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-S-[4-(2-amino-ethoxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 7.5 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(2-amino-ethoxy)- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol/conc. ammonia=100:50:1)=0.28; HPLC R_t=6.77 minutes; FAB-MS $(M+H)^+$=510.

The starting material is prepared analogously to Example 17a) using 5(S)-tert-butoxy-carbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-hydroxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)amide and iodoacctonitrile, with subsequent reduction of the nitrile function to the amino group with Raney nickel/H_2 under normal pressure and at 40° C. in ethanol in the presence of 4% ammonia.

EXAMPLE 69

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(5-amino-pentyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 22 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(5-amino-pentyloxy)- 3-(3-methoxypropyloxy)-phenyl]octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol/conc. ammonia=100:50: 1)=0.11; HPLC R_t=7.46 minutes; FAB-MS $(M+H)^+$=552.

The starting material is prepared analogously to Example 17a) using 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-hydroxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)amide and 5-iodovaleric acid nitrile, with subsequent reduction of the nitrile function to the amino group with Raney nickel/H_2 under normal pressure and at 40° C. in ethanol in the presence of 4% ammonia.

EXAMPLE 70

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(4-amino-butyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 36 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(4-amino-butyloxy)- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol/ammonia (conc.)=100:50:1)=0.15; HPLC R_t(I)=33.3 minutes; FAB-MS $(M+H)^+$=538.

The starting material is prepared analogously to Example 17a) using 5(S)-tert-butoxy-carbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-hydroxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)amide and 4-iodobutyronitrile, with subsequent reduction of the nitrile function to the amino group with Raney nickel/H_2 under normal pressure and at 40° C. in ethanol in the presence of 4% ammonia, to form 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(4-amino-butyloxy)- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide, R_f (dichloro-methane/methanol/conc. ammonia=100:50:1)=0.15, HPLC R_t=13.55 minutes.

EXAMPLE 71

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(4-N,N-dimethylamino-butyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 30 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(4-N,N-dimethylamino-butyloxy)- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol/ammonia (conc.)=100:50:1)=0.21; HPLC R_t=9.7 minutes; FAB-MS $(M+H)^+$=566.

The starting material is prepared by hydrogenation of 80 mg of 5(S)-tert-butoxycarbonyl-amino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(4-amino-butyloxy)-3-

(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)amide (Example 70), dissolved in 6 ml of methanol and in the presence of 25 ml of 35% formaldehyde solution, with 30 mg of 10% Pd/C for a period of 19 hours at room temperature and under normal pressure, and is purified by FC (5 g of silica gel, dichloromethane/methanol/ammonia (conc.)= 350:50: 1). R_f (dichloromethane/methanol/conc. ammonia= 350:50:1)=0.21; HPLC R_t=14.18 minutes; FAB-MS $(M+H)^+$=666.

EXAMPLE 72

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-{4-[4-N-(trifluoromethanesulfonylaminobutyloxy)-3-(3-methoxypropyloxy),phenyl]}-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 27 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-{ 4-[4-N-(trifluoromethanesulfonylaminobutyloxy)- 3-(3-methoxypropyloxy)-phenyl]}-octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol=9:1)= 0.27; HPLC R_t=14.67 minutes; FAB-MS $(M+H)^+$=670.

The starting material is prepared as follows:

a) 5(S)-Tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(4-N-trifluoromethanesulfonylamido-butyloxy)- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide

50 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl- 8-[4-(4-aminobutyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)-amide are dissolved in 4 ml of dichloromethane, and 23 ml of triethylamine and 13 ml of trifluoromethanesulfonic acid anhydride are added thereto at 0° C. The reaction mixture is stirred for 2 hours at room temperature and is then partitioned between dichloromethane (3x) and saturated $NaHCO_3$ solution (1x). The organic phases are combined, dried over magnesium sulfate and concentrated by evaporation. Purification of the residue by FC (15 g of silica gel, hexane/ethyl acetate=1:1) yields the title compound: R_f (hexane/ethyl acetate=1:1)=0.26; HPLC R_t=20.02 minutes.

EXAMPLE 73

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-carboxy-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 70 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-carboxy-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol=7:3)=0.35; HPLC R_t(I)=37.18 minutes; FAB-MS $(M+H)^+$=525.

The starting material is prepared analogously to Example 17a) using 5(S)-tert-butoxy-carbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-hydroxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)amide and bromoacetic acid benzyl ester, with subsequent debenzylation in ethanol with 10% Pd/C at room temperature and under normal pressure.

EXAMPLE 74

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(3-ethoxycarbonyl-propyloxy)-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)-amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 27 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(3-ethoxy-carbonylpropyloxy)- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol=9:1)=0.24; HPLC R_t=18.18 minutes; FAB-MS $(M+H)^+$=581.

The starting material is prepared analogously to Example 17a) using 5(S)-tert-butoxy-carbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-hydroxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)amide and 4-iodobutyric acid ethyl ester.

EXAMPLE 75

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(3-carboxypropyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 41 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(3-carboxypropyloxy)- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol=9:1)=0.20; HPLC R_t(I)=37.65 minutes; FAB-MS $(M+H)^+$=553.

The starting material is prepared from 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl- 2(R)-methyl-8-[4-(3-ethoxycarbonylpropyloxy)-3-(3-methoxypropyloxy)phenyl]-octanoic acid (N-butyl)amide (Example 74) by hydrolysis of the ester function in methanolic solution with 2 equivalents of 1N sodium hydroxide, by stirring for 24 hours at room temperature. The reaction mixture is concentrated by evaporation, an aqueous solution of the residue acidified to pH 4 is extracted with ethyl acetate, and the product obtained therefrom is purified by FC (dichloromethane/methanol=9:1). R_f (dichloromethane/methanol= 95:5)=0.41.

EXAMPLE 76

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(4-methoxy-carbonylbutyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 29 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(4-methoxy-carbonyl-butyloxy)- 3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol=9:1)=0.24; HPLC R_t(I)=42.55 minutes; FAB-MS $(M+H)^+$=581.

The starting material is prepared analogously to Example 17a) using 5(S)-tert-butoxy-carbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-hydroxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)amide and 5-iodovaleric acid methyl ester.

EXAMPLE 77

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(4-carboxy-butyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 10 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(4-carboxy-butyloxy)- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol=8:2)=0.34; HPLC R_t=9.92 minutes; FAB-MS $(M+H)^+$=567.

The starting material is prepared from 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy- 7(S)-isopropyl-2(R)-methyl-8-[4-(4-methoxycarbonyl-butyloxy)-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)amide (Example 76) by hydrolysis of the ester function in methanolic solution with 2 equivalents of 1N sodium hydroxide, by stirring for 24 hours at room temperature. The reaction mixture is concentrated by evaporation, the residue is dissolved in water, and the solution is acidified to pH 4 and extracted with ethyl acetate. The organic phases are dried over magnesium sulfate and concentrated by evaporation. Purification of the residue by FC (silica gel, dichloromethane/methanol=9:1) yields the title compound: R_f (dichloromethane/methanol/conc. ammonia=350:50:1)=0.14.

EXAMPLE 78

In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(3(R)-2-oxo-pyrrolidin-3-yl-methyl)]-amide hydrochloride,

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(3(S)-2-oxo-piperidin-3-yl-methyl)]-amide hydrochloride,

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(3(R)-2-oxo-piperidin- 3-yl-methyl)]-amide hydrochloride,

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(3-carbamoyl-3,3-dimethyl-propyl)]-amide hydrochloride,

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(4-methoxy-butyl)-phenyl]-octanoic acid [N-(5(S)-2-pyrrolidinon- 5-yl-methyl)]-amide hydrochloride,

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(4-methoxy-butyl)-phenyl]-octanoic acid [N-(5(R)-2-pyrrolidinon-5-yl-methyl)]-amide hydrochloride,

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(6(S)-2-oxo-piperidin-6-yl-methyl)]-amide hydrochloride,

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(6(R)-2-oxo-piperidin-6-yl-methyl)]-amide hydrochloride,

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-thiazol-2-yl-ethyl)]-amide dihydrochloride,

5(S)-amino-4(S)-hydroxy-2(S)-7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(4(S)-2-oxazolidinon-4-yl-methyl)]-amide hydrochloride,

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(4(R)-2-oxazolidinon-4-yl-methyl)]-amide hydrochloride,

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(3(S)-2,5-dioxo-pyrrolidin-3-yl-methyl)]-amide hydrochloride,

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(3(R)-2,5-dioxo-pyrrolidin-3-yl-methyl)]-amide hydrochloride,

5(S)-amino-4(S)-hydroxy-2(S)-7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2,6-dioxo-piperidin-4-yl-methyl)]-amide hydrochloride, or

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(4(S)-2-oxothiazolidin-4-yl-methyl)]-amide hydrochloride.

EXAMPLE 79

In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[3-(3-methoxypropoxy)- 4,5-ethylene-dioxy-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethyl-ethyl)-amide,

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)phenyl]-octanoic acid [N-(4(R)-2-oxothiazolidin-4-yl-methyl)]-amide hydrochloride,

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(tetrahydro-2-pyrimidon-5-yl-methyl)]-amide hydrochloride,

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(N-acetyl-2-amino-2-methyl-propyl)]-amide hydrochloride,

5(S)-amino-4(S)-hydroxy-2(S)-7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(N-formyl-2-amino-2-methyl-propyl)]-amide hydrochloride,

5(S)-amino-4(S)-hydroxy-2(S)-7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(4-acetyl-piperazinyl-ethyl)]-amide hydrochloride,

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2,4-imidazolinedion-5-yl-methyl)]-amide hydrochloride,

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(4-methoxy-butyl)-phenyl]-octanoic acid [N-(2-hydroxy-pyridin-6-yl-methyl)]-amide hydrochloride,

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2,2-dimethyl-2-sulfamoyl-ethyl)]-amide hydrochloride,

5(S)-amino-4(S)-hydroxy-2(S)-7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2,2-dimethyl-2-(N,N-dimethyl)-sulfamoyl-ethyl)]-amide hydrochloride,

5(S)-amino-4(S)-hydroxy-2(S)-7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-oxo-piperidin-3(R)-yl)]-amide hydrochloride,

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-oxo-piperidin-3(S)-yl)]-amide hydrochloride,

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-oxo-piperidin-4-yl)]-amide hydrochloride,

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(N-acetyl-piperidin-4-yl)]-amide hydrochloride, or

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(4-methoxy-but- 1-enyl)-phenyl]-octanoic acid [N-(2-carbamoyl-2,2-dimethyl-ethyl)]-amide hydrochloride.

EXAMPLE 80

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3- (3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 82 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S)-7(S)-diisopropyl-8-[4-(4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound: R_f (dichloromethane/methanol=9:1)=0.32; HPLC R_t(I)=42.32 minutes; FAB-MS $(M+H)^+$=509.

The starting material is prepared analogously to Examples 206a) and 200b) from 3-tert-butoxycarbonyl- 5(S)-[2(S)-carboxy-3-methyl-butyl]-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 200 c) and n-butylamine.

EXAMPLE 81

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(2-methoxymethoxyethyl)-phenyl]-octanoic acid (N-butyl)amide

50 mg of 5(S)-azido-4(S)-hydroxy-8(R,S)-isobutyroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(2-methoxymethoxyethyl)-phenyl]-octanoic acid (N-butyl)amide are hydrogenated in 10 ml of methanol in the presence of 50 mg of 10% Pd/C at room temperature and under normal pressure. The reaction mixture is filtered and concentrated by evaporation. The residue is purified by means of FC (2 g of silica gel, dichloromethane/methanol=9:1). The title compound is obtained: R_f (dichloromethane/methanol=9:1)= 0.19; HPLC R_t=13.42 minutes; FAB-MS $(M+H)^+$=509.

The starting material is prepared as follows:

a) 2-(2-Hydroxyethyl)-anisole

To a solution of 10 g of 2-(2-hydroxyphenyl)-ethanol in 200 ml of acetone there are added 35.3 g of Cs_2CO_3 and then a solution of 6.5 ml of methyl iodide in 40 ml of acetone. The reaction mixture is stirred for 50 minutes at room temperature, is filtered and is concentrated by evaporation. The residue is partitioned between diethyl ether and water. The organic phases are combined, dried over magnesium sulfate and concentrated by evaporation, and the residue is purified by means of FC (dichloromethane/diethyl ether= 97:3), yielding the title compound: R_f (dichloromethane/diethyl ether=97:3)=0.34; HPLC R_t=9.31 minutes.

b) 4-Bromo-2-(2-hydroxyethyl)-anisole

35.72 g of tetrabutylammonium tribromide am added in portions to a solution of 10.7 g of 2-(2-hydroxyethyl)-anisole in 195 ml of dichloromethane and 130 ml of methanol. The reaction mixture is stirred for 150 minutes at room temperature and is then concentrated by evaporation in a rotary evaporator. The residue is partitioned between diethyl ether and water. The organic phases are combined, dried over magnesium sulfate and concentrated by evaporation, and the residue is purified by means of FC (dichloromethane), yielding the title compound: R_f (dichloromethane)=0.26; HPLC R_t=13.04 minutes.

c) 4-Bromo-2-(2-methoxymethoxy-ethyl)-anisole

1.48 g of N-ethyl-diisopropylamine and 0.49 g of chlorodimethyl ether are added at room temperature to a solution of 948 mg of 4-bromo-2-(2-hydroxyethyl)-anisole in 30 ml of dichloromethane. The reaction mixture is stirred for 200 minutes at room temperature, and then 1 ml of water and 1 ml of 25% ammonium hydroxide solution are added thereto. The two-phase mixture is stirred vigorously for a further 15 minutes and then the organic phase is separated off, dried over sodium sulfate and concentrated by evaporation. Purification of the residue by means of FC (hexane/dichloromethane=1:1) yields the title compound: R_f (dichloromethane)=0.5; HPLC R_t=17.33 minutes.

d) 3(S)-Isopropyl-5(S)-{1(S)-azido-3(S)-isopropyl-4(R,S)-hydroxy-4-[4-methoxy- 3-(2-methoxymethoxyethyl)-phenyl]-butyl}-tetrahydrofuran-2-one

Several iodine crystals am added to a suspension of 763 mg of magnesium chips in 0.5 ml of tetrahydrofuran, and the mixture is activated in an ultrasound bath for 30 minutes. Then 4 drops of 1,2-dibromoethane and then a solution of 8.64 g of 4-bromo-2-(2-methoxymethoxyethyl)-anisole in 30 ml of tetrahydrofuran are added dropwise in such a manner that the reaction mixture boils under reflux. When the addition is complete, the mixture is maintained under reflux for a further one hour. The reaction mixture is then added dropwise within a period of 45 minutes, with stirring, to a solution, cooled to −75° C., of 2.85 g of 3(S)-isopropyl-5(S)-[1(S)-azido-3(S)-isopropyl-4-oxobutyl]-tetrahydrofuran- 2-one in 20 ml of tetrahydrofuran. The reaction mixture is stirred for a further 150 minutes at −75° C., and there are then added thereto, at the same temperature, a solution of 1.4 ml of glacial acetic acid in 1 ml of tetrahydrofuran and then 25 ml of saturated ammonium chloride solution. The reaction mixture is then brought to room temperature, poured onto 60 ml of water and extracted three times with 100 ml of ethyl acetate. The organic phases are washed with 50 ml of saturated sodium chloride solution, combined, dried over magnesium sulfate and concentrated by evaporation. Purification of the residue by means of FC (400 g of silica gel, hexane/ethyl acetate=8:2) yields the title compound: R_f (hexane/ethyl acetate=7:3)=0.25; HPLC R_t=48.10 and 50.29 minutes (diastereoisomeric mixture).

e) 3(S)-Isopropyl-5(S)-{1(S)-azido-3(S)-isopropyl-4(R,S)-isobutyryloxy-4-[4-methoxy- 3-(2-methoxymethoxyethyl)-phenyl]-butyl}-tetrahydrofuran-2-one

0.25 ml of pyridine, 0.31 ml of isobutyric acid anhydride and 15 mg of dimethylamino-pyridine are added to a solution of 300 mg of 3(S)-isopropyl-5(S)-{1(S)-azido-3(S)-isopropyl- 4(R,S)-hydroxy-4-[4-methoxy-3-(2-methoxymethoxyethyl)-phenyl]-butyl}-tetrahydrofuran- 2-one in 3.5 ml of dichloromethane, and the mixture is stirred for 80 hours at room temperature. The reaction mixture is then partitioned between dichloromethane (3x), water (1x) and saturated sodium chloride solution (2x). The combined organic phases are dried over magnesium sulfate and concentrated by evaporation, and the residue is purified by FC (30 g of silica gel, hexane/ethyl acetate=8:2), yielding the

title compound: R_f (hexane/ethyl acetate=8:2)=0.26; HPLC R_t=21.38 minutes and 21.76 minutes (diastereoisomeric mixture).

f) 5(S)-Azido-4(S)-hydroxy-2(S),7(S)-diisopropyl-8(R,S)-isobutyryloxy-8-[4-methoxy-3-(2-methoxymethoxyethyl)-phenyl]-octanoic acid (N-butyl)-amide

A solution of 170 mg of 3(S)-isopropyl-5(S)-{1(S)-azido-3(S)-isopropyl-4(R,S)-isobutyryloxy-4-[4-methoxy-3-(2-methoxymethoxyethyl)-phenyl]-butyl}-tetrahydrofuran-2-one in 1.4 ml of butylamine is stirred for 16 hours at room temperature and is then concentrated by evaporation. Purification of the residue by means of FC (hexane/ethyl acetate=7:3) yields the title compound: R_f (hexane/ethyl acetate=7:3)=0.25; HPLC R_t=20.38 and 20.8 minutes (diastereoisomeric mixture).

The 3(S)-isopropyl-5(S)-[1(S)-azido-3(S)-isopropyl-4-oxo-butyl]-tetrahydrofuran-2-one used in step d) is prepared as follows:

g) 2(S),7(S)-Diisopropyl-oct-4-ene-dicarboxylic acid [bis([4(S)-benzyl-oxazolidin-2-one)]-amide

48 ml of a 1.0M solution of lithium hexamethyldisilazide in tetrahydrofuran are added dropwise, with stirring, at −75° C., within a period of one hour, to a solution of 11.5 g of 4(S)-benzyl-3-isovaleroyl-oxazolidin-2-one in 32 ml of tetrahydrofuran. The mixture is stirred further for 2 hours at −75° C. and for 20 minutes at −20° C., and there are then added thereto 10 ml of 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidone (DMPU) and, within a period of 45 minutes, a solution of 4.28 g of 1,4-dibromo-2-butene in 10 ml of tetrahydrofuran. The reaction mixture is stirred for a further 15 hours at −20° C. and is then brought to 0° C. within a period of one hour; 10 ml of saturated ammonium chloride solution are then added thereto at −20° C. and, after 15 minutes, the mixture is brought to room temperature. The reaction mixture is then partitioned between dichloromethane and saturated sodium chloride solution/water=1:1. The organic phases are combined, dried over sodium sulfate and concentrated by evaporation, and the residue is purified by means of FC (hexane/ethyl acetate=4:1), yielding the title compound: R_f (hexane/ethyl acetate=4:1)=0.30; HPLC R_t=21.6 minutes; FAB-MS $(M+H)^+$=575; m.p.=110°–111° C. (crystallised from ethyl acetate/hexane).

h) 3(S)-Isopropyl-5(S)-{1(R)-bromo-4-methyl-3(S)-[(4(S)-benzyloxazolidin-2-on-3-yl)-carbonyl]-pentyl}-tetrahydrofuran-2-one

10.5 g of N-bromosuccinimide are added, with stirring, to a solution of 30 g of 2(S),7(S)-diisopropyl-oct-4-ene-dicarboxylic acid [bis(4(S)-benzyl-oxazolidin-2-one)]-amide in 360 ml of tetrahydrofuran and 120 ml of water, the temperature being maintained at room temperature with an ice-bath. The reaction mixture is stirred for a further 2 hours at room temperature, and then the tetrahydrofuran is evaporated off in a rotary evaporator. The aqueous residue is partitioned between diethyl ether (2×200 ml), water (2×50 ml) and saturated sodium chloride solution (1×50 ml). The organic phases are combined, dried over magnesium sulfate and concentrated by evaporation, and the residue is purified by means of FC (90 g of silica gel, hexane/ethyl acetate=3:1), yielding the title compound in the form of a crude product. Crystallisation from diisopropyl ether yields the pure compound: m.p.=91°–92° C.; R_f (hexane/ethyl acetate=8:2)=0.28; HPLC R_t=19.53 minutes; FAB-MS $(M+H)^+$=494.

i) 3(S)-Isopropyl-5(S)-{1(S)-azido-4-methyl-3(S)-[(4(S)-benzyl-oxazolidin-2-on-3-yl)-carbonyl]-pentyl}-tetrahydrofuran-2-one

13.6 g of freshly dried tetrabutylammonium azide are added to a solution, stirred at room temperature, of 17.8 g of 3(S)-isopropyl-5(S)-{1(R)-bromo-4-methyl-3(S)-[(4(S)-benzyl-oxazolidin-2-on-3-yl)-carbonyl]-pentyl}-tetrahydrofuran-2-one in 180 ml of toluene, and a further 10 g of the azide are added in the course of 160 hours' stirring at room temperature. The reaction mixture is then partitioned between ethyl acetate and water (2x) and saturated sodium chloride solution (1x). The organic phases are combined, dried over sodium sulfate and concentrated. The title compound is obtained from the evaporation residue by means of FC (hexane/ethyl acetate=8:2) and crystallisation from diethyl ether/hexane: m.p.=102°–103° C.; R_f (hexane/ethyl acetate=8:2)=0.2; HPLC R_t=18.55 minutes; FAB-MS $(M+H)^+$=457.

k) 3(S)-Isopropyl-5(S)-(1(S)-azido-3(S)-carboxy-4-methyl-pentyl)-tetrahydrofuran-2-one

175 ml of water, 74 ml of 30% hydrogen peroxide solution and 5.9 g of lithium hydroxide are slowly added in succession to a solution, stirred at −5° C., of 55.3 g of 3(S)-isopropyl-5(S)-{1(S)-azido-4-methyl-3(S)-[(4(S)-benzyl-oxazolidin-2-on-3-yl)-carbonyl]-pentyl}-tetrahydrofuran-2-one in 500 ml of tetrahydrofuran. The reaction mixture is stirred for one hour at 5° C. and for 150 minutes at room temperature, and then 750 ml of aqueous 1M sodium sulfite solution are added at 3° C. over a period of 30 minutes and the mixture is stirred for a further 30 minutes at room temperature. The reaction mixture is then freed of tetrahydrofuran by concentration, and the aqueous solution is washed three times with 1200 ml of ethyl acetate, the organic phases being back-extracted three times with 100 ml of 0.1N sodium hydroxide. The combined aqueous phases are adjusted to pH 1–2 with approximately 200 ml of 4N hydrochloric acid and are extracted with 3×1200 ml of ethyl acetate. The organic phases are combined, dried over magnesium sulfate and concentrated by evaporation, yielding the crude product which, for the purpose of cyclisation of the opened lactone, is dissolved in 500 ml of toluene and stirred for 2 hours at 50° C. with approximately 1 g of molecular sieve and approximately 1 g of p-toluenesulfonic acid. Filtration, concentration by evaporation and purification of the residue by means of FC (hexane/ethyl acetate/glacial acetic acid=30:60:1) yield the title compound, which crystallises spontaneously: m.p.=56°–58° C.; R_f (hexane/ethyl acetate/glacial acetic acid=30:60:1)=0.62; HPLC R_t=14.46 minutes; FAB-MS $(M+H)^+$=298.

l) 3(S)-Isopropyl-5(S)-(1(S)-azido-3(S)-isopropyl-4-oxo-butyl)-tetrahydrofuran-2-one

1.45 ml of oxalyl chloride are added dropwise at 0° C., with stirring, within a period of 10 minutes, to a solution of 1.7 g of 3(S)-isopropyl-5(S)-(1(S)-azido-3(S)-carboxy-4-methyl-pentyl)-tetrahydrofuran-2-one in 20 ml of toluene. 0.03 ml of dimethylformamide is then added, and the temperature is then increased to 37° C. within a period of 30 minutes. The reaction mixture is stirred for 2 hours at 37° C. and is then clarified by filtration and concentrated by evaporation under reduced pressure at a bath temperature of 30° C. The residue is twice dissolved in 10 ml of toluene and concentrated by evaporation again in the same manner. The crude acid chloride so obtained is dissolved in 5 ml of tetrahydrofuran, and 16 ml of a 0.34M solution of $NaAlH(O\text{-}tert\text{-}bu)_3$ in diglyme (H. C. Brown et al., J. Org. Chem. (1992) 58.472) are added thereto at −75° C. within a period of 30 minutes. The reaction mixture is stirred for 70 minutes at −75° C., and then a solution of 0.385 ml of glacial acetic acid in 1 ml of tetrahydrofuran is added dropwise at the same temperature, followed by 2.1 ml of saturated

NH_4Cl solution and then 20 ml of diethyl ether. The reaction mixture is brought to room temperature and is partitioned between diethyl ether and water/saturated sodium chloride solution. The organic phases are combined, dried over magnesium sulfate and concentrated by evaporation, and the residue is purified by means of FC (hexane/ethyl acetate= 95:5), yielding the title compound: R_f (hexane/ethyl acetate= 2:1)=0.55; HPLC R_t=16.41 minutes.

EXAMPLE 82

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-(3-hydroxypropyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-morpholinoethyl)amide hydrochloride

30 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-(3-hydroxypropyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-2-morpholino-ethyl)amide are dissolved in 1.5 ml of a 4N solution, cooled to 0° C., of hydrochloric acid in dioxane, and the mixture is then stirred for 10 minutes at 0° C. The reaction mixture is concentrated to dryness by evaporation under reduced pressure and at room temperature. Purification of the residue by means of FC (5 g of silica gel, dichloromethane/methanol=98:2) yields the title compound: R_f (dichloromethane/methanol=8:2)=0.20; R_t=10.43 minutes; FAB-MS $(M+H)^+$=610.

The starting material is prepared as follows:

a) 2-(3-Methoxypropyloxy)-phenol

A solution of 22 g of pyrocatechol in 80 ml of dimethylformamide is added at room temperature, within a period of 30 minutes, to a suspension of 8.4 g of NaH (60% dispersion in mineral oil) in 300 ml of dimethylformamide, and the mixture is stirred for one hour at room temperature. A solution of 49.3 g of 3-bromopropyl methyl ether in 80 ml of dimethylformamide is then added dropwise. The reaction mixture is stirred for a further 80 hours at room temperature and is then concentrated by evaporation under reduced pressure at a bath temperature of 30° C. The residue is partitioned between diethyl ether and water. The combined organic phases are dried over magnesium sulfate and concentrated by evaporation, and the residue is purified by FC (100 g of silica gel, hexane/dichloromethane=5:95), yielding the title compound: R_f (dichloromethane/diethyl ether= 96:4)=0.35; HPLC R_t=11.2 minutes.

b) 4-Bromo-2-(3-methoxypropyloxy)-phenol

6.9 g of tetrabutylammonium tribromide are added in portions, at room temperature, to a solution of 2.6 g of 2-(3-methoxypropyloxy)-phenol in 60 ml of dichloromethane and 40 ml of methanol, and the mixture is then stirred for 30 minutes. The reaction mixture is concentrated by evaporation and the residue is partitioned between diethyl ether and water. The combined organic phases are dried over magnesium sulfate and concentrated by evaporation, and the residue is purified by FC (700 g of silica gel, dichloromethane/diethyl ether=98:2), yielding the title compound: R_f (dichloromethane/diethyl ether=97:3)=0.50; HPLC R_t=14.32 minutes; FAB-MS $(M+H)^+$=262.

c) 4-(3-Benzyloxypropyloxy)-3-(3-methoxypropyloxy)-bromobenzene

A mixture of 4 g of 4-bromo-2-(3-methoxypropyloxy)-phenol, 2.3 g of potassium carbonate, 3.8 g of benzyl (3-bromopropyl) ether, a spatula tip of NaI and 15 ml of acetonitrile is stirred under reflux for 30 hours. The reaction mixture is filtered and the filtrate is concentrated by evaporation. The residue is partitioned between ethyl acetate and water. The organic phases are combined, dried over magnesium sulfate and concentrated by evaporation, and the residue is purified by means of FC (hexane/ethyl acetate= 95:5), yielding the title compound: R_f (hexane/ethyl acetate= 9:1)=0.15; HPLC R_t=20.66 minutes.

d) 3(S)-Isopropyl-5(S)-{1(S)-azido-3(S)-isopropyl-4(R,S)-hydroxy-4-[4-(3-benzyloxy-propyloxy)- 3-(3-methoxypropyloxy)-phenyl]-butyl}-tetrahydrofuran-2-one

1.3 ml of a 0.9M solution of butyllithium in hexane are slowly added dropwise to a solution, stirred at −75° C., of 500 mg of 4-(3-benzyloxypropyloxy)-3-(3-methoxypropyloxy)-bromobenzene in 2 ml of tetrahydrofuran. The reaction mixture is stirred for 20 minutes at −75° C., and then a suspension of magnesium bromide, freshly prepared from 44.5 mg of magnesium powder and 0.158 ml of 1,2-dibromoethane in 3 ml of tetrahydrofuran at room temperature, is added dropwise. The reaction mixture is stirred for a further 30 minutes at −75° C., and then a solution of 172 mg of 3(S)-isopropyl-5(S)-[1(S)-azido- 3(S)-isopropyl-4-oxo-butyl]-tetrahydrofuran-2-one in 2 ml of tetrahydrofuran is added dropwise. The mixture is again stirred for 30 minutes at −75° C., and then 1.2 ml of saturated ammonium chloride solution are added dropwise at the same temperature. The reaction mixture is brought to room temperature and is then extracted three times with ethyl acetate. The organic phases are washed with water (2x) and saturated sodium chloride solution (1x), dried over magnesium sulfate, combined and concentrated by evaporation, and the residue is purified by means of FC (2×30 g of silica gel, hexane/ethyl acetate=6:2), yielding the title compound: R_f (hexane/ethyl acetate=2:1)=0.23; HPLC R_t=20.27 and 21.07 minutes (diastereoisomeric mixture); FAB-MS M^+=611.

e) 3(S)-Isopropyl-5(S)-{1(S)-azido-3(S)-isopropyl-4(R,S)-acetoxy-4-[4-(3-benzyloxy-propyloxy)- 3-(3-methoxypropyloxy)-phenyl]-butyl}-tetrahydrofuran-2-one

A solution of 144 mg of 3(S)-isopropyl-5(S)-{1(S)-azido-3(S)-isopropyl-4(R,S)-hydroxy- 4-[4-(3-benzyloxypropyloxy)-3-(3-methoxypropyloxy)-phenyl]-butyl}-tetrahydrofuran- 2-one in 1.8 ml of acetic anhydride and 0.057 ml of pyridine is stirred for 30 hours at room temperature and is then concentrated to dryness by evaporation at room temperature and under reduced pressure. The residue is partitioned between dichloromethane (3x) and water/saturated sodium chloride solution (3x). The organic phases are combined, dried over magnesium sulfate and concentrated by evaporation, and the residue is purified by means of FC (hexane/ethyl acetate=4:1), yielding the title compound: R_f (hexane/ethyl acetate=2:1)=0.38 and 0.33; HPLC R_t=21.76 and 21.82 minutes (diastereoisomeric mixture); FAB-MS M^+=653, $(M+Na)^+$=676.

f) 3(S)-Isopropyl-5(S)-{1(S)-amino-3(S)-isopropyl-4-[4-(3-hydroxypropyloxy)- 3-(3-methoxypropyloxy)-phenyl]-butyl}-tetrahydrofuran-2-one

A solution of 151 mg of 3(S)-isopropyl-5(S)-{1(S)-azido-3(S)-isopropyl-4(R,S)-acetoxy- 4-[4-(3-benzyloxypropyloxy)-3-(3-methoxypropyloxy)-phenyl]-butyl}-tetrahydrofuran- 2-one in 10 ml of ethanol is hydrogenated under normal pressure and at room temperature in the presence of 70 mg of PdO for 170 hours. The reaction mixture is filtered and concentrated by evaporation, and the residue is dissolved in 10 ml of ethanol and is again hydrogenated for 24 hours in the presence of 140 mg of PdO under normal pressure and at room temperature. Filtration and concentration by evaporation yield the title compound in the form of a crude product: R_f (dichloromethane/methanol)=0.32;

HPLC R_f=11.72 minutes; FAB-MS $(M+H)^+$=480. The compound is used in the next step without being purified.

g) 3(S)-Isopropyl-5(S)-{1(S)-tert-butoxycarbonylamino-3(S)-isopropyl-4-[4-(3-hydroxy-propyloxy)-3-(3-methoxypropyloxy)-phenyl]-butyl}-tetrahydrofuran-2-one

To a solution, stirred at 0° C., of 106 mg of 3(S)-isopropyl-5(S)-{1(S)-amino-3(S)-isopropyl- 4-[4-(3-hydroxy-propyloxy)-3-(3-methoxypropyloxy)-phenyl]-butyl}-tetrahydrofuran- 2-one in 4.5 ml of dichloromethane there are added dropwise a solution of 0.07 ml of N-ethyldiisopropylamine in 0.1 ml of dichloromethane and then a solution of 77 mg of di-tert-butyl dicarbonate in 0.4 ml of dichloromethane. The reaction mixture is then brought to room temperature, is stirred at room temperature for 20 hours and is then concentrated to dryness by evaporation. Purification of the residue by means of FC (50 g of silica gel, dichloromethane/methanol=98:2) yields the title compound: R_f (dichloromethane/methanol=95:5)=0.34; HPLC R_t=19.07 minutes; FAB-MS M^+=579, $(M+Na)^+$=602.

h) 5(S)-Tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diispropyl-8-[4-(3-hydroxypropyloxy)- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-2-morpholinoethyl)amide

A mixture of 84 mg of 3(S)-isopropyl-5(S)-{1(S)-tert-butoxycarbonylamino-3(S)-isopropyl- 4-[4-(3-hydroxypropyloxy)-3-(3-methoxypropyloxy)-phenyl]-butyl}-tetrahydrofuran- 2-one, 0.6 ml of 4-(2-aminoethyl)-morpholine and 0.025 ml of glacial acetic acid is stirred for 16 hours at room temperature and for 6 hours at 45° C. and is then partitioned between diethyl ether (2x) and saturated $NaHCO_3$ solution (ix) and water (2x). The organic phases are combined, dried over magnesium sulfate and concentrated by evaporation, and the residue is purified by means of FC (5 g of silica gel, dichloromethane/methanol=98:2), yielding the title compound: R_f (dichloromethane/methanol=95:5)=0.16; HPLC R_t=14.49 minutes; FAB-MS $(M+H)^+$=710.

EXAMPLE 83

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethyl-ethyl)-amide semifumarate

20 g of ice and 12 ml of 2N NaOH are added in succession to a stirred solution of 2.35 g of 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethyl-ethyl)-amide hydrochloride (Example 137) in 20 ml of water, and the mixture is then extracted with 3×50 ml of tert-butyl methyl ether. The combined organic phases are dried with magnesium sulfate and concentrated by evaporation. 0.232 g of fumaric acid is added to the evaporation residue in 25 ml of methanol. The mixture is stirred until a clear solution has formed and is then concentrated by evaporation. The residue is crystallised from 100 ml of acetonitrile/ethanol=95:5. The crystals are filtered off with suction and dried at 60° C. The title compound is obtained in the form of a white powder having a melting point of 95°–104° C.

EXAMPLE 84

5(S)-Amino-2(S),7(S)-diisopropyl-4(S)-hydroxy-8-[4-tert-butyl-3-(3-methoxypropoxy)-phenyl]-octanoic acid [N-2-(morpholin-4-yl)-ethyl]-amide dihydrochloride

A 4N hydrochloric acid solution in dioxane (20 ml) is added at 0°–5° C. to 768 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-tert-butyl-3-(3-methoxypropoxy)-phenyl]-octanoic acid [N-2-(morpholin-4-yl)-ethyl]-amide, and the mixture is then stirred for one hour. The solvent is then removed by lyophilisation under a high vacuum, the residue is dissolved in anhydrous dichloromethane and filtered over cotton wool, and the filtrate is concentrated. A small amount of 4N hydrochloric acid in dioxane is again added to the residue, the resulting solution is lyophilised, and the residue is dried under a high vacuum. The title compound is obtained in the form of a white amorphous solid: R_f (dichloromethane/methanol/conc. ammonia=9:1:0.1)=0.23; HPLC R_t=14.5 minutes; FAB-MS $(M+H)^+$=592.

The starting materials are prepared as follows:

a) 5(S)-Tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-tert-butyl-3-(3-methoxypropoxy)-phenyl]-octanoic acid [N-2-(morpholin-4-yl)-ethyl]-amide

A solution of 756 mg of 3(S)-isopropyl-5(S)-{1(S)-tert-butoxycarbonylamino-3(S)-isopropyl- 4-[4-tert-butyl-3-(3-methoxypropoxy)-phenyl]-butyl}-tetrahydrofuran-2-one in 4 ml of 4-(2-aminoethyl)-morpholine and 0.23 ml of glacial acetic acid is stirred for 4 hours at 65° C. and is then concentrated by evaporation. The residue is partitioned between diethyl ether (30 ml) and a saturated sodium hydrogen carbonate solution (10 ml), the aqueous phase is extracted with diethyl ether (2×30 ml), and the combined organic phases are dried over magnesium sulfate and concentrated. Purification of the residue by means of FC (70 g of silica gel, dichloromethane/methanol/conc. ammonia=98:2:1 after 96:4:1) yields the title compound in the form of a white foam: R_f (dichloromethyane/methanol/conc. ammonia=9:1:0.1)=0.43; HPLC R_t=19.8 minutes.

b) 3(S)-Isopropyl-5(S)-{1(S)-tert-butoxycarbonylamino-3(S)-isopropyl-4-[4-tert-butyl- 3-(3-methoxypropoxy)-phenyl]-butyl}-tetrahydrofuran-2-one

A solution of 1.24 g of 3(S)-isopropyl-5(S)-{4(R,S)-acetoxy-1(S)-azido-3(S)-isopropyl- 4(R,S)-[4-tert-butyl-3-(3-methoxypropoxy)-phenyl]-butyl}-tetrahydrofuran-2-one in 25 ml of ethanol is hydrogenated for a period of 28 hours in the presence of 2.4 g of 5% PdO/C (Engelhardt) at room temperature and under normal pressure. The reaction mixture is filtered over Celite 545 and washed with ethanol, and the residue obtained after concentration is dried under a high vacuum. The product so obtained (843 mg) is dissolved in 20 ml of dichloromethane, and 0.58 ml of N-diisopropylethylamine and a solution of 638 mg of di-tert-butyl dicarbonate in 5 ml of dichloromethane are added thereto in succession at 0°–5° C. The mixture is stirred at room temperature overnight, and then the solvent is removed in vacuo and the crude product is purified by means of FC (60 g of silica gel, hexane/ethyl acetate/conc. ammonia=80:20:1). The title compound is obtained in the form of a colourless oil: R_f (hexane/ethyl acetate/conc. ammonia=50:50:1)=0.90; HPLC R_t=26.2 minutes.

c) 3(S)-Isopropyl-5(S)-{4(R,S)-acetoxy-1(S)-azido-3(S)-isopropyl-4(R,S)-[4-tert-butyl- 3-(3-methoxypropoxy)-phenyl]-butyl}-tetrahydrofuran-2-one

A mixture of 1.15 g of 3(S)-isopropyl-5(S)-{4(R,S)-hydroxy-1(S)-azido-3(S)-isopropyl- 4(R,S)-[4-tert-butyl-3-(3-methoxypropoxy)-phenyl]-butyl}-tetrahydrofuran-2-one, 11 ml of acetic anhydride and 0.55 ml of pyridine is stirred overnight at room temperature. The reaction mixture is concentrated and the residue is partitioned between 100 ml of dichloromethane and 20 ml of water. The crude product obtained after working up by extraction is purified by FC (80 g of silica gel, hexane/ethyl acetate=2:1). The title com-

pound is obtained in the form of a yellowish oil: R_f (hexane/ethyl acetate=2:1)=0.66.

d) 3(S)-Isopropyl-5(S)-{4(R,S)-hydroxy-1(S)-azido-3(S)-isopropyl-4(R,S)-[4-tert-butyl- 3-(3-methoxypropoxy)-phenyl]-butyl}-tetrahydrofuran-2-one

In a manner analogous to that described in Example 185c), 4-tert-butyl-3-(3-methoxy-propoxy)-bromobenzene (2.35 g), dissolved in 60 ml of tetrahydrofuran, is reacted with 4.86 ml of a 1N n-butyllithium solution (in hexane) and then with a suspension of magnesium bromide in 20 ml of tetrahydrofuran (prepared from 380 mg of magnesium powder and 1.35 ml of 1,2-dibromoethane in). A solution of 1.46 g of 3(S)-isopropyl- 5(S)-[1(S)-azido-3(S)-isopropyl-4-oxobutyl]-tetrahydrofuran-2-one in 6 ml of tetrahydrofuran is added dropwise to the resulting suspension at −70° C. over a period of 20 minutes, and the mixture is then stirred for a further one hour. After working up by extraction, the crude product is purified by FC (300 g of silica gel, hexane/ethyl acetate=5:1 after 3:1). The title compound is obtained in the form of a pale yellow oil: R_f (hexane/ethyl acetate=2:1)=0.57; HPLC R_t=22.9 and 24.1 minutes (diastereoisomeric mixture).

e) 4-Tert-butyl-3-(3-methoxypropoxy)-bromobenzene

A suspension of 2.60 g of 5-bromo-2-tert-butyl-phenol, 4.34 g of 3-methoxypropyl bromide and 5.55 g of caesium carbonate in 40 ml of acetone is stirred at 60° C. overnight. After cooling to room temperature, the mixture is filtered and the crude product obtained after concentration of the filtrate is purified by means of FC (80 g of silica gel, hexane/ethyl acetate=98:2). The title compound is obtained in the form of an oil: R_f (hexane/ethyl acetate=9:1)=0.56.

EXAMPLE 85

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(4-hydroxypiperidin-1-yl)ethyl]amide dihydrochloride

100 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(4-hydroxy-piperidin- 1-yl)-ethyl]-amide are dissolved in 3 ml of 4N hydrochloric acid in dioxane at 0° C., and the mixture is stirred for 2 hours at 0° C. The reaction mixture is lyophilised and the title compound is obtained: R_f (dichloromethane/methanol=8:2)=0.08; HPLC R_t= 8.85 minutes; FAB-MS $(M+H)^+$=552.

The starting material is prepared as follows:

a) 5(S)-Tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(4-hydroxypiperidin-1-yl)-ethyl]-amide

102 mg of 2-{1(S)-tert-butoxycarbonylamino-3(S)-isopropyl-4-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-butyl}- 4(R)-methyl-tetrahydrofuran-5-one (Example 105e) and 0.5 g of N-(2-aminoethyl)-4-hydroxypiperidine are stirred for 2 hours at 80° C. The reaction mixture is purified by means of FC (60 g of silica gel, dichloromethane/methanol=4:1). The title compound is obtained: R_f (dichloromethane/methanol=4:1)=0.16.

EXAMPLE 86

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2,2-dimethyl-2-morpholino-ethyl)amide dihydrochloride

Analogously to Example 85, the title compound is obtained starting from 120 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2,2-dimethyl-2-morpholino-ethyl)-amide: R_f (dichloromethane/methanol=9:1)=0.07; HPLC R_t=9.22 minutes; FAB-MS $(M+H)^+$=566.

The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxycarbonylamino- 3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and 4-(2-amino-1,1-dimethyl-ethyl)-morpholine.

EXAMPLE 87

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(trans-2,6-dimethyl-morpholino)-ethyl]amide dihydrochloride

Analogously to Example 85, the title compound is obtained starting from 102 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(trans-2,6-dimethyl-morpholino)-ethyl]amide: R_f (dichloromethane/methanol=8:2)=0.27; HPLC R_t=9.56 minutes; FAB-MS $(M+H)^+$=566.

The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxycarbonylamino- 3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and 4-(2-aminoethyl)-trans- 2,6-dimethyl-morpholine.

a) 4-(2-Amino-ethyl)-2,6-(trans)-dimethyl-morpholine

8.20 g of 4-(2-phthaloylaminoethyl)-trans-2,6-dimethyl-morpholine are stirred under reflux for 2 hours in 250 ml of ethyl alcohol with 2.76 ml of hydrazine hydrate. The reaction mixture is diluted with diethyl ether and then clarified by filtration. The filtrate is concentrated, yielding the crude title compound: R_f (dichloromethane/methanol/conc. ammonia=40:10:1)=0.21.

b) 4-(2-Phthaloylaminoethyl)-trans-2,6-dimethyl-morpholine

10.16 g of N-(2-bromoethyl)-phthalimide and 11.50 g of trans-2,6-dimethylmorpholine are stirred for 30 minutes at 130° C. The reaction mixture is then partitioned between ice-water and ethyl acetate. The organic phases are concentrated by evaporation and the residue is purified by means of FC (240 g of silica gel, ethyl acetate/hexane=1:2). The title compound is obtained: R_f (ethyl acetate/hexane=1:2)=0.39.

EXAMPLE 88

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(cis-2,6-dimethyl-morpholino)ethyl]-amide dihydrochloride

Analogously to Example 85, the title compound is obtained starting from 97 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-

methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(cis-2,6-dimethyl-morpholino)-ethyl]amide: R_f (dichloromethane/methanol=8:2)=0.21; HPLC R_t=9.38 minutes; FAB-MS $(M+H)^+$=566.

The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxycarbonylamino- 3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and 4-(2-amino-ethyl)-cis-2,6-dimethyl-morpholine.

The 4-(2-amino-ethyl)-cis-2,6-dimethyl-morpholine is prepared analogously to Examples 87 a) and 87 b) from cis-2,6-dimethylmorpholine.

EXAMPLE 89

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-piperidinoethyl)amide dihydrochloride

Analogously to Example 85, the title compound is obtained staging from 74 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-piperidinoethyl)amide: R_f (dichloromethane/methanol=8:2)=0.09; HPLC R_t=9.55 minutes; FAB-MS $(M+H)^+$ =536.

The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxycarbonylamino- 3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and N-(2-piperidinoethyl)amine.

EXAMPLE 90

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(4-methoxypiperidino)-ethyl]-amide dihydrochloride

Analogously to Example 85, the title compound is obtained starting from 74 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(4-methoxy-piperidino)ethyl]-amide: R_f (dichloromethane/methanol=8:2)=0.12; HPLC R_t=9.39 minutes; FAB-MS $(M+H)^+$=566.

The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxycarbonylamino- 3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and 1-(2-aminoethyl)-4-methoxypiperidine.

The 1-(2-amino-ethyl)-4-methoxypiperidine is prepared analogously to Examples 87 a) and 87 b) from 4-methoxypiperidine.

EXAMPLE 91

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-thiomorpholinoethyl)amide dihydrochloride

Analogously to Example 85, the title compound is obtained starting from 110 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-thiomorpholino-ethyl)amide: R_f (dichloromethane/methanol=8:2)=0.17; HPLC R_t=9.53 minutes; FAB-MS $(M+H)^+$=554.

The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxy-carbonylamino- 3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and 4-(2-aminoethyl)thiomorpholine.

EXAMPLE 92

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3- (3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-hydroxypropyl)]amide hydrochloride

Analogously to Example 85, the title compound is obtained starting from 110 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-hydroxypropyl)]amide: R_f (dichloromethane/methanol=9:1)=0.07; HPLC R_t=9.65 minutes; FAB-MS $(M+H)^+$ =483.

The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxycarbonylamino- 3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4-(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and 3-amino-1-propanol.

EXAMPLE 93

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(4-hydroxybutyl)]amide hydrochloride

Analogously to Example 85, the title compound is obtained starting from 112 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(4-hydroxybutyl)]amide: R_f (dichloro-methane/methanol=9:1)=0.07; HPLC R_t=9.83 minutes; FAB-MS $(M+H)^+$ =497.

The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxycarbonylamino- 3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4-(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and 4-amino-1-butanol.

EXAMPLE 94

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(4-acetoxybutyl)]amide hydrochloride

Analogously to Example 85, the title compound is obtained starting from 27 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(4-acetoxybutyl)]amide: R_f (dichloromethane/methanol= 9:1)= 0.16; HPLC R_t=11.53 minutes; FAB-MS $(M+H)^+$= 539.

The starting material is prepared as follows:

a) 5(S)-Tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy- 3-(3-methox-

ypropyloxy)-phenyl]-octanoic acid [N-(4-acetoxybutyl)]amide

30 ml of triethylamine, 2 mg of 4-(N,N'-dimethylamino)pyridine (DMAP) and 20 ml of acetic anhydride are added at 0° C. to 116 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy- 7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(4-hydroxybutyl)]amide (Example 93) in 5 ml of tetrahydrofuran. The reaction solution is stirred for 18 hours at room temperature. The reaction mixture is partitioned between diethyl ether and water/saturated sodium chloride solution. The organic phases are concentrated by evaporation and the residue is purified by FC (40 g of silica gel, eluant: dichloromethane/methanol=95:5). The title compound is obtained: R_f (dichloromethane/methanol=9:1)=0.60.

EXAMPLE 95

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-cyanopropyl)]amide hydrochloride

Analogously to Example 85, the title compound is obtained starting from 107 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-cyanopropyl)]amide: R_f (dichloromethane/methanol=9:1)=0.07; HPLC R_t=10.76 minutes; FAB-MS $(M+H)^+$=492.

The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxycarbonylamino- 3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and 4-amino-butyronitrile.

EXAMPLE 96

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3- (3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-methoxypropyl)]amide hydrochloride

Analogously to Example 85, the title compound is obtained starting from 107 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-methoxypropyl)]amide: R_f (dichloromethane/methanol=8:2)=0.34; HPLC R_t=10.70 minutes; FAB-MS $(M+H)^+$=497.

The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxycarbonylamino- 3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and 3-methoxy-propylamine.

EXAMPLE 97

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-acetylamino-ethyl)]amide hydrochloride

Analogously to Example 85, the title compound is obtained starting from 82 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-acetylamino-ethyl)]amide: R_f (dichloromethane/methanol=8:2)=0.17; HPLC R_t=9.54 minutes; FAB-MS $(M+H)^+$=510.

The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxy-carbonylamino- 3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and N-acetyl-ethylenediamine.

EXAMPLE 98

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(2-pyridyl)-ethyl]}-amide hydrochloride

Analogously to Example 85, the title compound is obtained starting from 118 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(2-pyridyl)-ethyl]}-amide: R_f (dichloromethane/methanol=9:1)=0.09; HPLC R_t=8.88 minutes; FAB-MS $(M+H)^+$=530.

The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxycarbonylamino- 3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and 2-(2-aminoethyl)-pyridine.

EXAMPLE 99

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(N'-oxomorpholino)ethyl]-amide hydrochloride

Analogously to Example 85, the title compound is obtained starting from 82 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(N'-oxomorpholino)ethyl]amide: R_f (dichloromethane/methanol=8:2)=0.07; HPLC R_t=9.04 minutes; FAB-MS $(M+H)^+$=554.

The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxycarbonylamino- 3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and 4-(2-aminoethyl)-N-oxo-morpholine.

The starting material is prepared as follows:

a) 4-(2-Aminoethyl)-N-oxo-morpholine

2.8 g of 4-(2-benzyloxycarbonylaminoethyl)-N-oxo-morpholine are hydrogenated in the presence of 0.30 g of 10% Pd/C in methanol for 10 minutes at room temperature and under normal pressure. The reaction mixture is filtered and concentrated by evaporation. The crude title compound is obtained: ^{1}H-NMR (CD_3OD), δ(ppm)=4.90 (2H, s), 4.20 (1H, m), 3.87–2.80 (10H, m), 2.50 (1H, m)

b) 4-(2-Benzyloxycarbonylaminoethyl)-N-oxo-morpholine

6 portions, each of 1.48 ml, of 30% hydrogen peroxide are added at 60° C., with stirring, at intervals of 12 hours, to 10.6 g of 4-(2-benzyloxycarbonylaminoethyl)-morpholine in 12 ml of methanol. Saturated sodium sulfite solution is added carefully to the cooled reaction mixture until the excess peroxide has been destroyed. The methanol is evaporated off, and the resulting suspension is taken up in ethyl acetate/methanol 99:1. The mixture is dried with magnesium sulfate

and is filtered, and the filtrate is concentrated by evaporation. Crystallisation from ethyl acctate yields the title compound: R_f (dichloromethane/methanol=8:2)=0.17; m.p. 163° C.

EXAMPLE 100

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[3-(tert-butylsulfonyl)-propyl]}-amide hydrochloride

Analogously to Example 85, the title compound is obtained starting from 110 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[3-(tert-butylsulfonyl)-propyl]}-amide: R_f (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.45; HPLC R_t=11.27 minutes; FAB-MS $(M+H)^+$=587.

The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxycarbonylamino- 3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and 3-amino-1-(tert-butylsulfonyl)propane.

The starting material is prepared as follows:

a) 3-Amino-1-(tert-butylsulfonyl)-propane

1.0 g of 3-aminopropyl-(tert-butylsulfonyl)-propane is dissolved at 0° C. in 30 ml of water. 2.14 g of potassium permanganate and 2 ml of 4N hydrochloric acid in 30 ml of water are added in succession, and the mixture is stirred overnight at 0° C. The dark suspension is filtered off and washed with 100 ml of hot water. 50 ml of toluene are added to the filtrate, and the mixture is concentrated. The precipitated white crystals are purified by means of FC (10 g of silica gel, ethyl acetate/methanol/cone. ammonia=80:15:5). The title compound is obtained: R_f (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.20.

EXAMPLE 101

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[3;(ethylsulfonyl)-propyl]}-amide hydrochloride

Analogously to Example 85, the title compound is obtained starting from 44 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[3-(ethylsulfonyl)-propyl]}-amide: R_f (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.26; HPLC R_t=10.40 minutes; FAB-MS $(M+H)^+$=559.

The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxycarbonylamino- 3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and 3-amino-1-(ethylsulfonyl)propane.

The starting material is prepared as follows:

a) 3-Amino-1-(ethylsulfonyl)-propane

1.0 g of 3-aminopropyl-ethyl sulfide is placed in 35 ml of methanol at 0° C.; 15.5 g of oxone in 35 ml of water are added and the mixture is stirred at 0° C. for 4 hours. 200 ml of water are added and the mixture is extracted with 3 x 150 ml of dichloromethane. The organic extracts are concentrated by evaporation and purified by FC (10 g of silica gel, ethyl acetate/methanol/conc. ammonia=80: 15:5). The title compound is obtained: R_f (ethyl acetate/methanol/conc. ammonia=80: 15:5)=0.15.

EXAMPLE 102

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(ethylsulfonyl)-ethyl]}-amide hydrochloride

Analogously to Example 85, the title compound is obtained starting from 90 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)- isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(ethylsulfonyl)-ethyl]}-amide: R_f (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.39; HPLC R_t=10.50 minutes; FAB-MS $(M+H)^+$=545.

The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxycarbonylamino- 3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and 2-amino-1-(ethylsulfonyl)ethane.

EXAMPLE 103

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(N-butylsulfonyl)-ethyl]}-amide hydrochloride

Analogously to Example 85, the title compound is obtained starting from 67 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)- isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(N-butylsulfonyl)-ethyl]}-amide: R_f (ethyl acetate/methanol/conc. ammonia=80: 15:5)=0.41; HPLC R_t=12.52 minutes; FAB-MS $(M+H)^+$=588.

The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxycarbonylamino- 3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and 2-aminoethyl-(N-butyl)sulfonamide.

EXAMPLE 104

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(N,N-dimethylsulfonyl)-ethyl]}-amide hydrochloride

Analogously to Example 85, the title compound is obtained starting from 120 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(N,N-dimethylsulfonyl)-ethyl]}-amide: R_f (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.43; HPLC R_t=11.03 minutes; FAB-MS $(M+H)^+$=560.

The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxycarbonylamino- 3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and 2-aminoethyl-(N,N-dimethyl)sulfonamide.

EXAMPLE 105

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-carbamoyl-propyl)]-amide hydrochloride

84 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-carbamoyl-propyl)]-amide are dissolved in 3 ml of 4N hydrochloric acid in dioxane at 0° C. and the mixture is stirred for 2 hours at 0° C. The reaction mixture is lyophilised. The title compound is obtained: R_f (dichloromethane/methanol=9:1)=0.04; HPLC R_t=9.44 minutes; HR FAB-MS $(M+H)^+$=510.

The starting materials are prepared as follows:

a) 5(S)-Tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-carbamoyl-propyl)]-amide

50 mg of tetrabutylammonium fluoride trihydrate are added to 115 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-tert-butyldimethylsilyloxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy- 3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(3-carbamoyl-propyl)]-amide in 4 ml of dimethylformamide at 0° C. The reaction mixture is stirred for a further 5 hours at room temperature and then concentrated by evaporation. 20 ml of saturated sodium hydrogen carbonate solution are added to the evaporation residue and the mixture is extracted repeatedly with ethyl acetate. The organic phases are washed with saturated sodium chloride solution and concentrated by evaporation. The residue is purified by means of FC (18 g of silica gel, dichloromethane/methanol=9:1). The title compound is obtained: R_f (dichloromethane/methanol=9:1): 0.24.

b) 5(S)-Tert-butoxycarbonylamino-4(S)-tert-butyldimethylsilyloxy-7(S)-isopropyl-2(R)-methyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-carbamoyl-propyl)]-amide

67 µl of triethylamine, 34 mg of 4-aminobutyric acid amide hydrochloride and 38 µl of cyanophosphonic acid diethyl ester are added in succession to 128 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-tert-butyldimethylsilyloxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid in 8 ml of dimethylformamide at 0° C. The reaction mixture is stirred for a further 18 hours at room temperature. The reaction mixture is concentrated by evaporation and 20 ml of 10% citric acid solution and ice are added to the residue. The mixture is extracted repeatedly with ethyl acetate and the organic phases are then washed with saturated sodium hydrogen carbonate solution and saturated sodium chloride solution. After concentration by evaporation, the residue is purified by means of FC (70 g of silica gel, dichloromethane/methanol=9:1). The title compound is obtained: R_f (dichloromethane/methanol=9:1)=0.38.

c) 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyldimethylsilyloxy-7(S)-isopropyl-2(R)-methyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid

4.45 g of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid (crude) are stirred in 45 ml of dimethylformamide with 2.36 g of tert-butyldimethylsilyl chloride and 2.03 g of imidazole for 6 days at room temperature. The mixture is concentrated by evaporation and the residue is partitioned between 10% citric acid solution and ethyl acetate. The organic phase is concentrated and stirred in 20 ml of tetrahydrofuran, 8 ml of water and 20 ml of acetic acid at room temperature for 16 hours. After concentration by evaporation, ice/water is added to the residue and the mixture is then extracted with ethyl acetate. The title compound is obtained from the organic phase after FC (260 g of silica gel, ethyl acetate/hexane=1:1): R_f (ethyl acetate/hexane=1:1)=0.32.

d) 5(S)-Tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid

28.5 ml of 1N lithium hydroxide solution are added to 3.6 g of 2-{1(S)-tert-butoxycarbonylamino- 3(S)-isopropyl-4-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one in 210 ml of 1,2-dimethoxyethane/water (2:1) at room temperature. The reaction mixture is stirred at room temperature for a further 1 hour and then concentrated by evaporation. Ice and 10% aqueous citric acid solution are added to the residue. Repeated extraction with chloroform yields the crude title compound: R_f (ethyl acetate/hexane=1:1)=0.05; HPLC R_t=16.41 minutes.

e) 2-{1(S)-tert-butoxycarbonylamino-3(S)-isopropyl-4-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-butyl}- 4(R)-methyl-tetrahydrofuran-5-one

2.02 g of p-toluenesulfonic acid (monohydrate) are added to 5.6 g of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)-amide (Example 32) in 240 ml of chloroform at room temperature and the mixture is stirred at room temperature for a further 18 hours. The reaction mixture is concentrated by evaporation and the residue is partitioned between diethyl ether and 0.1N hydrochloric acid. The organic phases are concentrated by evaporation and the title compound is obtained from the residue after FC (160 g of silica gel, eluant: ethyl acetate/hexane 1:1): R_f (ethyl acetate/hexane=2:1)=0.47; m.p. 86°–87° C.

EXAMPLE 106

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[3-(1H-tetrazol-5-yl)-propyl]}-amide hydrochloride

Analogously to Example 105, the title compound is obtained starting from 47 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[3-(1H-tetrazol-5-yl)-propyl]}-amide and after lyophilisation: R_f (dichloromethane/methanol=8:2)=0.46; HPLC R_t=9.97 minutes; FAB-MS $(M+H)^+$=535.

The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyldimethylsilyloxy-7(S)-isopropyl-2(R)-methyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 3-(1H-tetrazol-5-yl)-propylamine.

EXAMPLE 107

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[3-(1H-imidazol-5-yl)-propyl]}-amide hydrochloride

Analogously to Example 105, the title compound is obtained starting from 43 mg of 5(S)-tert-butoxycarbony-

lamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[3-(1H-imidazol-5-yl)-propyl]}-amide and after lyophilisation: R_f (dichloromethane/methanol=8:2)=0.13; HPLC R_t=8.83 minutes; FAB-MS $(M+H)^+$=533.

The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyldimethylsilyloxy-7(S)-isopropyl-2(R)-methyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 3-(1H-imidazol-5-yl)-propylamine.

EXAMPLE 108

5(S)-Amino-4(S)-hydroxy-7-(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-3-(3-methyl-1,2,4-oxadiazol-5-yl)-propyl]}-amide hydrochloride

Analogously to Example 105, the title compound is obtained starting from 140 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[3-(3-methyl-1,2,4-oxadiazol-5-yl)-propyl]}-amide and after lyophilisation: R_f (dichloromethane/methanol=9:1)=0.12; HPLC R_t=11.05 minutes; FAB-MS $(M+H)^+$=549.

The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyldimethylsilyloxy-7(S)-isopropyl-2(R)-methyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 3-(3-methyl-1,2,4-oxadiazol-5-yl)-propylamine.

a) 3-(3-Methyl-1,2,4-oxadiazol-5-yl)-propylamine

272 mg of 3-methyl-5-[3-(N-phthaloylamino)propyl]-1,2,4-oxadiazole in 10 ml of ethyl alcohol are stirred for 2 hours under reflux with 146 ml of hydrazine hydrate. The reaction mixture is diluted with diethyl ether and then clarified by filtration. The filtrate is concentrated by evaporation and yields the crude title compound: R_f (dichloromethane/methyl alcohol/conc. ammonia=40:10:1)=0.37.

b) 3-Methyl-5-[3-(N-phthaloylamino)propyl]-1,2,4-oxadiazole

0.84 g of sodium hydride dispersion (80%) is added to 2.08 g of acetamidoxime in 200 ml of tetrahydrofuran at room temperature and the mixture is stirred at 60° C. for 2 hours. A solution of 2.47 g of 4-(N-phthaloylamino)butyric acid methyl ester in 30 ml of tetrahydrofuran is then added and stirring is continued at 60° C. for a further 3 hours. The reaction mixture is poured onto 1N hydrochloric acid/ice and extracted repeatedly with ethyl acetate. The dried organic phases are concentrated by evaporation and the residue is boiled in 60 ml of xylene for 3 hours on a water-separator. The solvent is evaporated off and the title compound is obtained from the residue after FC (40 g of silica gel, ethyl acetate/hexane=1:1): R_f (ethyl acetate/hexane=1:1)=0.26.

EXAMPLE 109

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-aminopropyl)]-amide dihydrochloride

Analogously to Example 105, the title compound is obtained starting from 125 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-tert-butoxycarbonylamino-propyl)]-amide and after lyophilisation: R_f (dichloromethane/methanol/conc. ammonia=40:10:1)=0.08; HPLC R_t=6.48 minutes; FAB-MS $(M+H)^+$=482.

The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyldimethylsilyloxy-7(S)-isopropyl-2(R)-methyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 3-tert-butoxycarbonylamino-propylamine.

EXAMPLE 110

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-dimethylamino-ethyl)]-amide dihydrochloride

Analogously to Example 105, the title compound is obtained starting from 38 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-dimethylamino-ethyl)]-amide and after lyophilisation: R_f (dichloromethane/methanol/conc. ammonia=350:50:1)=0.03; HPLC R_t=8.61 minutes; FAB-MS $(M+H)^+$=496.

The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyldimethylsilyloxy-7(S)-isopropyl-2(R)-methyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 2-dimethylaminoethylamine.

EXAMPLE 111

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-morpholinoethyl)amide dihydrochloride

Analogously to Example 105, the title compound is obtained starting from 70 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-morpholinoethyl)amide and after lyophilisation: R_f (dichloromethane/methanol/conc. ammonia=350:50:1)=0.15; HPLC R_t=8.74 minutes; FAB-MS $(M+H)^+$=538.

The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyldimethylsilyloxy-7(S)-isopropyl-2(R)-methyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 4-(2-aminoethyl)-morpholine.

EXAMPLE 112

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(3-morpholinopropyl)amide dihydrochloride

Analogously to Example 105, the title compound is obtained starting from 37 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(3-morpholinopropyl)amide and after lyophilisation: R_f (dichloromethane/methanol/conc. ammonia=350:50:1)=

0.11; HPLC R_f=8.68 minutes; FAB-MS $(M+H)^+$=552.

The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyldimethylsilyloxy-7(S)-isopropyl-2(R)-methyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 4-(3-aminopropyl)-morpholine.

EXAMPLE 113

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(1,1-dioxothiomorpholino)ethyl]amide dihydrochloride

Analogously to Example 105, the title compound is obtained starting from 100 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(1,1-dioxothiomorpholino)ethyl]-amide and after lyophilisation: R_f (dichloromethane/methanol=8:2)=0.30; HPLC R_f=9.29 minutes; FAB-MS $(M+H)^+$=586.

The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyldimethylsilyloxy-7(S)-isopropyl-2(R)-methyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 2-(1,1-dioxothiomorpholino)-ethylamine.

EXAMPLE 114

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-ethoxycarbonylethyl)amide hydrochloride

Analogously to Example 105, the title compound is obtained starting from 32 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-ethoxycarbonyl-ethyl)]-amide and after lyophilisation: R_f (dichloromethane/methanol=9:1)=0.17; HPLC R_f=11.31 minutes; FAB-MS $(M+H)^+$=525.

The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyldimethylsilyloxy-7(S)-isopropyl-2(R)-methyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and β-alanine ethyl ester hydrochloride.

EXAMPLE 115

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carboxy-ethyl)]-amide hydrochloride

Analogously to Example 105, the title compound is obtained starting from 60 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carboxy-ethyl)]-amide and after lyophilisation: R_f (dichloromethane/methanol=8:2)=0.28; HPLC R_f=9.74 minutes; FAB-MS $(M+H)^+$=497.

The starting material is prepared as follows:

a) 5(S)-Tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carboxy-ethyl)]-amide

70 mg of 5(S)-tert-butoxyamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-ethyloxy-carbonylethyl)]-amide (Example 114) are stirred in 2 ml of methanol with 224 µl of 1N sodium hydroxide at room temperature for 18 hours. After evaporation of the methanol, 250 µl of 1N hydrochloric acid are added and the product is extracted with ethyl acetate. The organic phase is concentrated by evaporation and the residue is purified by means of FC (10 g of silica gel, eluant: dichloromethane/methanol=8:2). The title compound is obtained: R_f (dichloromethane/methanol=9:1)=0.12.

EXAMPLE 116

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-methoxycarbonyl-ethyl)]-amide hydrochloride

Analogously to Example 105, the title compound is obtained starting from 90 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-methoxycarbonyl-ethyl)]-amide and after lyophilisation: R_f (dichloromethane/methanol=9:1)=0.13; HPLC R_f=10.80 minutes; FAB-MS $(M+H)^+$=525.

The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyldimethylsilyloxy-7(S)-isopropyl-2(R)-methyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 4-aminobutyric acid methyl ester hydrochloride.

EXAMPLE 117

(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-carboxypropyl)]-amide hydrochloride

Analogously to Example 105, the title compound is obtained starting from 38 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-carboxypropyl)]-amide and after lyophilisation: R_f (dichloromethane/methanol=8:2)=0.55; HPLC R_f=9.85 minutes; FAB-MS $(M+H)^+$=511.

The starting material is prepared as follows:

5(S)-Tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-carboxypropyl)]-amide

Analogously to Example 115 a), the title compound is prepared from 5(S)-tert-butoxycarbonyl-amino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(3-methyloxycarbonylpropyl)]-amide (Example 116).

EXAMPLE 118

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carbamoylethyl)]-amide hydrochloride

Analogously to Example 105, the title compound is obtained starting from 93 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carbamoylethyl)]-amide and after lyophilisation: R_f (dichloromethane/methanol=8:2)=0.15; HPLC R_t=9.33 minutes; FAB-MS $(M+H)^+$=496.

The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyldimethylsilyloxy-7(S)-isopropyl-2(R)-methyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 3-aminopropionic acid amide hydrochloride.

EXAMPLE 119

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(4-carbamoylbutyl)-amide hydrochloride

Analogously to Example 105, the title compound is obtained starting from 85 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(4-carbamoylbutyl)]-amide and after lyophilisation: R_f (dichloromethane/methanol=8:2)=0.20; HPLC R_t=9.72 minutes; FAB-MS $(M+H)^+$=524.

The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyldimethylsilyloxy-7(S)-isopropyl-2(R)-methyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 5-aminopentanoic acid amide hydrochloride.

EXAMPLE 120

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[3-(N-methylcarbamoyl)propyl]amide hydrochloride

Analogously to Example 105, the title compound is obtained starting from 89 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[3-(N-methylcarbamoyl)propyl]amide and after lyophilisation: R_f (dichloromethane/methanol=9:1)=0.04; HPLC R_t=9.74 minutes; FAB-MS $(M+H)^+$=524.

The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyldimethylsilyloxy-7(S)-isopropyl-2(R)-methyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 4-amino-N-methyl-butyric acid amide hydrochloride.

EXAMPLE 121

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-{3-[N-(2-methoxyethyl)carbamoyl]propyl}-amide hydrochloride

Analogously to Example 105, the title compound is obtained starting from 92 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-{3-[N-(2-methoxyethyl)carbamoyl]propyl}-amide and after lyophilisation: R_f (dichloromethane/methanol=8:2)=0.28; HPLC R_t=10.14 minutes; FAB-MS $(M+H)^+$=568.

The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyldimethylsilyloxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 4-aminobutyric acid N-(2-methoxyethyl)amide hydrochloride.

The starting material is prepared as follows:

4-Aminobutyric acid N-(2-methoxyethyl)amide hydrochloride

2.95 g of 4-benzyloxycarbonylaminobutyric acid N-(2-methoxyethyl)amide are hydrogenated in the presence of 0.24 g of 10% Pd/C in 150 ml of methanol and 100 ml of 0.1N hydrochloric acid for 2 hours at room temperature and under normal pressure. The reaction mixture is filtered and concentrated by evaporation. The crude title compound is obtained: ^1H NMR (CD_3OD), δ(ppm)=4.92(4H, s), 3.53–3.20 (4H, m), 3.34 (3H, 2.96 (2H, t, J=12 Hz), 2.37 (2H, t, J=12 Hz), 1.93 (2H, m).

b) 4-Benzyloxycarbonylaminobutyric acid N-(2-methoxyethyl)amide 5.02 g of 4-benzyloxycarbonylaminobutyric acid methyl ester are stirred under reflux in 35 ml of ethanol with 15 ml of 2-methoxyethylamine for 5 days. The reaction mixture is concentrated by evaporation and the residue is purified by means of FC (240 g of silica gel, dichloromethane/methanol=95:5). The title compound is obtained: R_f (dichloromethane/methanol=95:5)=0.33.

EXAMPLE 122

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(4-morpholino-4-oxo-butyl)amide hydrochloride

Analogously to Example 105, the title compound is obtained staring from 110 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(4-morpholino-4-oxo-butyl)amide and after lyophilisation: R_f (dichloromethane/methanol=9:1)=0.06; HPLC R_t=10.17 minutes; FAB-MS $(M+H)^+$=580.

The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyldimethylsilyloxy-7(S)-isopropyl-2(R)-methyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 4-aminobutyric acid N'-(4-morpholino)amide hydrochloride.

EXAMPLE 123

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-2,2-dimethyl-ethyl)]-amide hydrochloride

Analogously to Example 105, the title compound is obtained starting from 66 mg of 5(S)-tert-butoxycarbony-lamino- 4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-2,2-dimethyl-ethyl)]-amide and after lyophilisation: R_f (dichloromethane/methanol=8:2)=0.27; HPLC R_t=12.10 minutes; FAB-MS $(M+H)^+$=524.

The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyldimethylsilyloxy-7(S)- isopropyl-2(R)-methyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 3-amino-2,2-dimethyl-propionic acid amide hydrochloride.

EXAMPLE 124

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-morpholinoethyl)amide dihydrochloride

3.09 g of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-morpholinoethyl)amide are dissolved in 40 ml of 4N hydrochloric acid in dioxane at 0° C. and the solution is stirred at 0° C. for 2 hours. The reaction mixture is lyophilised and the title compound is obtained: R_f (dichloromethane/methanol=8:2)=0.27; HPLC R_t=9.52 minutes; HR FAB-MS $(M+H)^+$=566.

The starting materials are prepared as follows:

a) 5(S)-Tert-butoxycarbonylamino-4(S)-hydroxy-2(S), 7(S)-diisopropyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-morpholino-ethyl)amide

1.30 g of p-toluenesulfonic acid (monohydrate) are added to 4.18 g of 3-tert-butoxycarbonyl- 5(S)-{2(S)-[N-(2-morpholino-ethyl)carbamoyl]-2(S)-isopropyl-ethyl}-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl- 1,3-oxazolidine in 160 ml of methanol at 0° C. The reaction solution is stirred at room temperature for a further 18 hours. After evaporation of the solvent, 200 ml of 0.1N sodium hydroxide are added to the residue and extraction is carried out with dichloromethane. The organic extracts are concentrated by evaporation and purified by FC (230 g of silica gel, dichloromethane/methanol=95:5). The title compound is obtained: R_f (dichloromethane/methanol=9:1)=0.55.

b) 3-Tert-butoxycarbonyl-5(S)-{2(S)-[N-(2-morpholino-ethyl)-carbamoyl]- 2(S)-isopropyl-ethyl}- 4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}- 2,2-dimethyl-1,3-oxazolidine

1.09 ml of triethylamine, 1.02 ml of 4-(2-aminoethyl)-morpholine and 1.19 ml of cyanophosphonic acid diethyl ester are added in succession to 3.88 g of 3-tert-butoxycarbonyl- 5(S)-[2(S)-carboxy-3-methyl-butyl]-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-2,3-oxazolidine in 190 ml of dimethylformamide at 0° C. The reaction mixture is stirred at room temperature for a further 18 hours. The reaction mixture is concentrated by evaporation and the residue is partitioned between diethyl ether and saturated sodium hydrogen carbonate solution. The organic phases are washed with saturated sodium chloride solution and concentrated by evaporation. The residue is purified by FC (230 g of silica gel, dichloromethane/methanol=95:5). The title compound is obtained: R_f (dichloromethane/methanol=95:5)=0.25.

c) 3-Tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl- 3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine

53 g of 3-tert-butoxycarbonyl-5(S)-(2(S)-formyl-3-methyl-butyl)-4(S)-{2(S)-isopropyl- 3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine are dissolved in 470 ml of toluene, and, at 0° C., 470 ml of water, 79.1 g of potassium permanganate and 9.7 g of tetrabutylammonium bromide are added in succession thereto. The reaction mixture is stirred for a further 48 hours at 0°–5° C., and then, at 10° C., 1.2 liters of 10% sodium sulfite solution are added. After a further 30 minutes, 1.95 liters of 10% citric acid solution and 1.2 liters of water are added. The product is extracted by repeated extraction with ethyl acetate. The extracts are concentrated by evaporation and purified by FC (2.3 kg of silica gel, ethyl acetate/hexane=3:7). The title compound is obtained: R_f (ethyl acetate/hexane=1:2)=0.21.

d) 3-Tert-butoxycarbonyl-5(S)-(2(S)-formyl-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine

100 g of molecular sieve (0.3 nm) and 16.6 g of N-methylmorpholine-N-oxide are added to 53 g of 3-tert-butoxycarbonyl-5(S)-(3-hydroxy-2(S)-isopropyl-propyl)-4(S)-{2(S)-isopropyl- 3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine in 1.8 liters of dichloromethane at room temperature. The reaction mixture is stirred for 10 minutes and then 1.60 g of tetrapropylammonium perrutherate are added. The reaction mixture is stirred for a further 30 minutes and then filtered. The filtrate is diluted with dichloromethane and then washed in succession with 2M sodium sulfite solution, saturated sodium chloride solution and 1M copper(II) sulfate. The organic phase is concentrated by evaporation and the crude title compound is obtained: R_f (ethyl acetate/hexane=1:2)=0.43.

e) 3-Tert-butoxycarbonyl-5(S)-(3-hydroxy-2(S)-isopropyl-propyl)-4(S)-2(S)-isopropyl- 3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine

3.7 g of 3-tert-butoxycarbonyl-5(S)-(3-benzyloxy-2(S)-isopropyl-propyl)-4(S)-{2(S)-isopropyl- 3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine are hydrogenated in the presence of 1.0 g of 5% Pd/C in 50 ml of tetrahydrofuran for 15 minutes at room temperature and under normal pressure. The reaction mixture is filtered and concentrated by evaporation. The residue is purified by means of FC (140 g of silica gel, ethyl acetate/hexane=1:2). The title compound is obtained: R_f (ethyl acetate/hexane=1:2)=0.28.

f) 3-Tert-butoxycarbonyl-5(S)-(3-benzyloxy-2(S)-isopropyl-propyl)-4(S)-{2(S)-isopropyl- 3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (A)

and

3-tert-butoxycarbonyl-5(R)-(3-benzyloxy-2(S)-isopropyl-propyl-4(S)-{2(S)-isopropyl- 3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (B)

10.9 ml of 2,2-dimethoxypropane and 10 mg of p-toluenesulfonic acid (monohydrate) are added to 7.0 g of 5(S)-tert-butoxycarbonylamino-4(R,S)-hydroxy-2(S),7(S)-diisopropyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octyl-benzyl ether in 1.86 liters of dichloromethane at room temperature. The reaction mixture is stirred at room temperature for a further 24 hours. After concentration by evaporation, the residue is purified by FC (1 kg of silica gel and dichloromethane/diethyl ether=96:4). The title compounds are obtained:

A) R_f (dichloromethane/tert-butyl methyl ether)=0.36

B) R_f (dichloromethane/tert-butyl methyl ether)=0.44

g) 5(S)-Tert-butoxycarbonylamino-4(R,S)-hydroxy-2(S), 7(S)-diisopropyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octyl-benzyl ether

51.1 g of magnesium chips are placed in 1.4 liters of tetrahydrofuran at 55° C. A solution of 380 g of 2(S)-bromomethyl-3-methyl-butyl-benzyl ether, 30.2 ml of 1,2-dibromoethane in 0.8 liter of tetrahydrofuran at 55° C. is added dropwise over a period of 30 minutes. The reaction mixture is stirred for a further 20 minutes at 55° C. and then cooled to 5° C. A solution of 190 g of 2(S)-tert-butoxycarbonylamino-4(S)-isopropyl-5-[4-methoxy-3-(3-methyoxypropyloxy)-phenyl]-pentanal in 0.7 liter of tetrahydrofuran is then added dropwise. The reaction mixture is stirred for a further 3 hours at room temperature, and then, at 5° C., saturated ammonium chloride solution is added and extraction is carried out with diethyl ether. The extracts are concentrated by evaporation and purified by FC (4 kg of silica gel, ethyl acetate/hexane=1:3). The title compound is obtained in the form of a diastereoisomeric mixture: R_f (ethyl acetate/hexane=1:2)=0.26; HPLC R_t=22.67 and 22.81 (40:60).

h) 2(S)-Tert-butoxycarbonylamino-4(S)-isopropyl-5-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-pentanal

The title compound is prepared analogously to Example 1 c) to 1 g), except that in step 1 g) instead of 2(S)-isopropyl-3-(p-tert-butyl-phenyl)-propanol there is used 2(R)-isopropyl- 3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propanol. That compound is prepared as follows:

i) 2(R)-Isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propanol

186 g of 2(R)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propionic acid in 0.5 liter of tetrahydrofuran are added dropwise at room temperature to a stirred mixture of 27.2 g of sodium borohydride in 1.5 liters of tetrahydrofuran. After 45 minutes a solution of 76.2 g of iodine in 1 liter of tetrahydrofuran is added dropwise. The reaction mixture is stirred for 4 days and then 1 liter of methanol is carefully added dropwise. After evaporation of the solvent the residue is taken up in 2 liters of 2N hydrochloric acid and extracted repeatedly with ethyl acetate. The organic extracts are washed in succession with water, saturated sodium thiosulfate solution, water/saturated sodium chloride solution (1:1), 0.1N sodium hydroxide solution and saturated sodium chloride solution. The organic extracts are concentrated by evaporation and purified by FC (2.4 kg of silica gel, ethyl acetate/hexane=1:4). The title compound is obtained: R_f (ethyl acetate/hexane=1:1)=0.28.

k) 2(R)-Isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propionic acid

0.434 liter of 30% hydrogen peroxide is slowly added to 300 g of 4(R)-benzyl-3-{2(S)-isopropyl- 3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propionyl}-oxazolidin-2-one in 4.8 liters of tetrahydrofuran/water (3:1) at 0° C. After the addition of 31.2 g of lithium hydroxide, the mixture is stirred for 3 hours at 0°–20° C. 2.55 liters of 1.5M sodium sulfite solution are then added to the reaction mixture at 0°–15° C. and stirring is continued for a further 30 minutes. 1 liter of saturated sodium hydrogen carbonate solution is added and the tetrahydrofuran is evaporated off. The aqueous solution is washed repeatedly with dichloromethane and then acidified with 2N hydrochloric acid (pH 3.0). Extraction with dichloromethane and subsequent evaporation of the solvent yield the title compound: R_f (ethyl acetate/hexane=2:1)=0.30; m.p. 43.5°–44° C.

l) 4(R)-Benzyl-3-{2(R)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propionyl}-oxazolidin- 2-one

600 ml of tetrahydrofuran are added to a solution of 600 ml of 1M lithium hexamethyl-disilazide and the mixture is stirred at −70° C. Then a solution of 156.6 g of 4(R)-benzyl-3-isovaleroyl-oxazolidin-2-one in 500 ml of tetrahydrofuran is added dropwise and the reaction mixture is stirred for a further 75 minutes at −70° C. Then a solution of 145 g of 4-methoxy-3-(3-methoxypropyloxy)-benzyl bromide in 500 ml of tetrahydrofuran is added dropwise. The temperature of the reaction mixture is allowed to rise from −70° to 0° C. over a period of 2 hours. The reaction mixture is left to stand for a further 18 hours at 4° C. and then, with stirring, 250 ml of saturated ammonium chloride solution are added. The tetrahydrofuran is evaporated off and the residue is extracted with ethyl acetate. The title compound is obtained from the residue of the extracts by purification by means of FC (2.4 kg of silica gel, ethyl acetate/hexane=1:1): R_f (ethyl acetate/hexane=1:2)=0.30; m.p. 55°–56° C.

m) 4-Methoxy-3-(3-methoxypropyloxy)-benzyl bromide

97 ml of trimethylbromosilane are added, with stirring at room temperature, to 113.1 g of 4-methoxy-3-(3-methoxypropyloxy)-benzyl alcohol in 1.31 liters of chloroform. After 10 minutes the solvent is evaporated off and the residue is immediately purified by means of FC (900 g of silica gel, eluant: ethyl acetate/hexane 1:3). The title compound is obtained: R_f (ethyl acetate/hexane=1:2)=0.34; m.p. 50°–51 ° C.

n) 4-Methoxy-3-(3-methoxypropyloxy)-benzyl alcohol

7.7 g of 3-hydroxy-4-methoxy-benzyl alcohol, 10.35 g of potassium carbonate and 12.1 g of 1-bromo-3-methoxypropane are stirred under reflux in 150 ml of acetone for 3 days. After evaporation of the solvent, water is added to the residue and extraction is carried out with ethyl acetate. After evaporation of the solvent the title compound is obtained from the organic extracts by means of FC (240 g of silica gel, dichloromethane/methanol=96:4): R_f (ethyl acetate/hexane=2:1)=0.31.

EXAMPLE 125

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(3-morpholinopropyl)amide dihydrochloride

Analogously to Example 124, the title compound is obtained starting from 120 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-(3-morpholinopropyl)amide: R_f (dichloromethane/methanol/conc. ammonia=350:50:1)=0.12; HPLC R_t=9.64 minutes; FAB-MS $(M+H)^+$=580.

The starting material is prepared analogously to Example 124 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-meth-

oxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 4-(3-aminopropyl)morpholine.

EXAMPLE 126

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2,2-dimethyl-2-morpholino-ethyl)amide dihydrochloride

Analogously to Example 124, the title compound is obtained starting from 110 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S)-7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-(2,2-dimethyl-2-morpholino-ethyl)amide: R_f (dichloromethane/methanol=9:1)=0.05; HPLC R_t=10.35 minutes; FAB-MS $(M+H)^+$=594.

The starting material is prepared analogously to Example 124 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 4-(2-amino-1, 1-dimethyl-ethyl)-morpholine.

a) 4-(2-Amino-1,1-dimethyl-ethyl)-morpholine

A solution of 8.33 g of 2-methyl-2-morpholino-propionic acid amide in 50 ml of tetrahydrofuran is slowly added at room temperature to 3.33 g of lithium aluminium hydride in 85 ml of tetrahydrofuran. The reaction mixture is then stirred for a further 2 hours under reflux. The reaction mixture is cooled and then 5 ml of water, 6.67 ml of 2N sodium hydroxide and a further 5 ml of water are added in succession. The suspension is clarified by filtration and the crude title compound is obtained from the concentrated filtrate: ^1H NMR ($CDCl_3$), δ(ppm)=3.67 (4H, m), 2.52(2H, s), 2.48 (4H, m), 1.37 (2H, bs), 0.92 (6H, s).

b) 2-Methyl-2-morpholino-propionic acid amide

272 ml of concentrated sulfuric acid are slowly added, with stirring, to 57.9 g of 2-methyl-2-morpholino-propionitrile (exothermic reaction). After the addition of 43 ml of water, the mixture is stirred for 2 hours at 100°–110° C. The reaction mixture is cooled to 50° C. and added dropwise at 0° C. to a solution of 846 ml of 20% ammonia in 242 ml of water. The mixture is then extracted repeatedly with dichloromethane. The organic phases are washed with saturated sodium chloride solution and with sodium sulfate. The crude title compound is obtained from the concentrated filtrate: 1H NMR ($CDCl_3$), δ(ppm)=7.08 (1H, bs), 5.38 (1H, bs), 3.72(4H, m), 2.53 (4H, m), 1.22(6H, s)

EXAMPLE 127

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-thiomorpholinoethyl)amide dihydrochloride

Analogously to Example 124, the title compound is obtained starting from 110 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-(2-thiomorpholinoethyl)amide: R_f (dichloromethane/methanol=8:2)=0.33; HPLC R_t=10.39 minutes; FAB-MS $(M+H)^+$=582.

The starting material is prepared analogously to Example 124 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 4-(2-aminoethyl)thiomorpholine.

EXAMPLE 128

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(1,1-dimethyl-2-morpholino-ethyl)amide dihydrochloride

Analogously to Example 124, the title compound is obtained staging from 95 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-(1,1-dimethyl-2-morpholino-ethyl)amide: R_f (dichloromethane/methanol=8:2)=0.42; HPLC R_t=10.37 minutes; FAB-MS $(M+H)^+$=594.

The starting material is prepared analogously to Example 124 a) and 130 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 4-(2-amino-2,2-dimethyl-ethyl)-morpholine.

EXAMPLE 129

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[1(R,S)-methyl-2-morpholino-ethyl]amide dihydrochloride

Analogously to Example 124, the title compound is obtained starting from 73 mg of 5(S)-tert-butoxycarbonylamino- 4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-[1(R,S)-methyl-2-morpholino-ethyl]amide: R_f (dichloromethane/methanol=8:2)=0.43; HPLC R_t=9.98/10.58 minutes; FAB-MS $(M+H)^+$=580.

The starting material is prepared analogously to Example 124 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 4-(2-amino-2(R,S)-methyl-ethyl)-morpholine.

EXAMPLE 130

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1-carbamoyl-1-methyl-ethyl)]-amide hydrochloride

1.5 ml of trifluoroacetic acid are added to 56 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy- 2(S)-7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1-carbamoyl-1-methyl-ethyl)]-amide in 1.5 ml of dichloromethane at 0° C. The mixture is stirred for a further 30 minutes at 0° C. The reaction mixture is poured onto cooled 1N sodium hydroxide and the product is extracted repeatedly with dichloromethane. The organic phases are dried, and ethereal hydrochloric acid is added.

Concentration by evaporation yields the title compound: R_f (dichloromethane/methanol=8:2)=0.30; HPLC R_t=11.25; FAB-MS $(M+H)^+$=538.

The starting materials are prepared as follows:

a) 5(S)-Tert-butoxycarbonylamino-4(S)-hydroxy-2(S), 7(S)-diisopropyl-8-4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1-carbamoyl-1-methyl-ethyl)]-amide

5 mg of p-toluenesulfonic acid (monohydrate) are added to 82 mg of 3-tert-butoxycarbonyl- 5(S)-{2-[N-(1-carbamoyl-1-methyl-ethyl)-carbamoyl]-2(S)-isopropyl-ethyl}-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl- 1,3-oxazolidine in 5 ml of methanol at 0° C. The reaction solution is stirred for a further 18 hours at room temperature. After evaporation of the solvent, 20 ml of saturated sodium hydrogen carbonate solution are added to the residue and extraction is carried out repeatedly with ethyl acetate. The organic extracts are concentrated by evaporation and purified by means of FC (35 g of silica gel, dichloromethane/methanol=9:1). The title compound is obtained: R_f (dichloromethane/methanol=9:1)=0.47.

b) 3-Tert-butoxycarbonyl-5(S)-{2-[N-(1-carbamoyl-1-methyl-ethyl)-carbamoyl]- 2(S)-isopropyl-ethyl}-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}- 2,2-dimethyl-1,3-oxazolidine

106 µl of 4-methyl-morpholine, 66 mg of 2-aminoisobutyric acid amide hydrochloride and 91 mg of O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) are added in succession to 119 mg of 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy- 3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}- 2,2-dimethyl-1,3-oxazolidine (Example 124c) in 8 ml of dimethylformamide. The reaction mixture is stirred for 8 days at 40° C. The mixture is concentrated by evaporation and the residue is partitioned between ethyl acetate and saturated sodium chloride solution. The organic phases are concentrated by evaporation and the residue is purified by means of FC (60 g of silica gel, dichloromethane/methanol=95:5). The title compound is obtained: R_f (dichloromethane/methanol=95:5)=0.30.

EXAMPLE 131

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[3-(N-methylcarbamoyl)-propyl]}-amide hydrochloride

The title compound is obtained analogously to Example 124 staffing from 101 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[3-(N-methylcarbamoyl)-propyl]}-amide: R_f (dichloromethane/methanol=8:2)=0.32; HPLC R_t=10.11 minutes; FAB-MS $(M+H)^+$=552.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 4-amino-N-methylbutyric acid amide hydrochloride.

EXAMPLE 132

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[3-(N,N-dimethylcarbamoyl)-propyl]}-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 91 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[3-(N,N-dimethylcarbamoyl)-propyl]}-amide: R_f (dichloromethane/methanol=8:2)=0.36; HPLC R_t=10.38 minutes; FAB-MS $(M+H)^+$=566.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 4-amino-N,N-dimethylbutyric acid amide hydrochloride.

EXAMPLE 133

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(N,N-dimethylcarbamoyl)ethyl]amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 87 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3methoxypropyloxy)-phenyl]-octanoic acid N-[2-(N,N-dimethylcarbamoyl)ethyl]-amide: R_f (dichloromethane/methanol=8:2)=0.38; HPLC R_t=10.31 minutes; FAB-MS $(M+H)^+$=552.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3-amino-N,N-dimethylpropionic acid amide hydrochloride.

EXAMPLE 134

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1-carbamoylmethyl)]-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 84 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1-carbamoylmethyl)]-amide: R_f (dichloromethane/methanol=8:2)=0.20; HPLC R_t=9.73 minutes; FAB-MS $(M+H)^+$=510.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and glycinamide hydrochloride.

EXAMPLE 135

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carbamoylethyl)]-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 78 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoylethyl)amide: R_f (dichloromethane/methanol=8:2)=0.24; HPLC R_t=9.87 minutes; FAB-MS $(M+H)^+$=524.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl- 5(S)-[2(S)-carboxy-3-methyl-butyl]-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3-aminopropionic acid amide hydrochloride.

EXAMPLE 136

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(3-carbamoylpropyl)amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 74 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(3-carbamoylpropyl)amide: R_f (dichloromethane/methanol=9:1)=0.06; HPLC R_t=10.27 minutes; FAB-MS $(M+H)^+$=538.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 4-aminobutyric acid amide hydrochloride.

EXAMPLE 137

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethyl-ethyl)amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 94 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethyl-ethyl)amide: R_f (dichloromethane/methanol=8:2)=0.33; HPLC R_t=11.26 minutes; FAB-MS $(M+H)^+$ =552.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3-amino-2,2-dimethylpropionic acid amide hydrochloride.

EXAMPLE 138

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2,2-dimethyl-2-(N-methylcarbamoyl)ethyl]amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 87 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2,2-dimethyl-2-(N-methylcarbamoyl)-ethyl]}-amide: R_f (dichloromethane/methanol=8:2)=0.40; HPLC R_t=11.69 minutes; FAB-MS $(M+H)^+$=566.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3-amino-2,2-dimethyl-N-methylpropionic acid amide hydrochloride.

a) 3-Amino-2,2-dimethyl-N-methylpropionic acid amide hydrochloride

Analogously to Example 121 a) from 3-benzyloxycarbonylamino-2,2-dimethyl-N-methyl-propionic acid amide.

b) 3-Benzyloxycarbonylamino-2,2-dimethyl-N-methyl-propionic acid amide

4.19 g of 3-benzyloxycarbonylamino-2,2-dimethylpropionic acid ethyl ester and 50 ml of 33% methylamine (in ethanol) are stirred for 8 days at 60° C. in a bomb tube. The reaction mixture is concentrated by evaporation and the residue is purified by FC (220 g of silica gel, dichloromethane/methanol=95:5). The title compound is obtained: R_f (dichloromethane/methanol=9:1)=0.51.

c) 3-Benzyloxycarbonylamino-2,2-dimethylpropionic acid ethyl ester

31 ml of 90% chloroformic acid benzyl ester are slowly added, at 0°–5° C., to 29.04 g of 3-amino-2,2-dimethylpropionic acid ethyl ester in 500 ml of ethyl acetate and 250 ml of 1M sodium hydrogen carbonate solution. The reaction mixture is stirred for 2 hours at 0°–5° C. and extracted with ethyl acetate. The organic phases are washed with saturated sodium chloride solution and then concentrated. The evaporation residue is purified by FC (1 kg of silica gel; eluant: ethyl acetate/hexane= 1:3). The title compound is obtained: R_f (ethyl acetate/hexane=1:3)=0.28.

EXAMPLE 139

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(N-methylcarbamoyl)ethyl]amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 92 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(N-methylcarbamoyl)-ethyl]amide: R_f (dichloromethane/methanol=8:2)=0.24; HPLC R_t=10.40 minutes; FAB-MS $(M+H)^+$ =538.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3-amino-N-methylpropionic acid amide hydrochloride.

EXAMPLE 140

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(3-morpholino-3-oxopropyl)amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 99 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-

methoxypropyloxy)-phenyl]-octanoic acid N-(3-morpholino-3-oxopropyl)amide: R_f (dichloromethane/methanol=8:2)=0.51; HPLC R_t=11.35 minutes; FAB-MS $(M+H)^+$ =594.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3-aminopropionic acid morpholide hydrochloride.

EXAMPLE 141

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoyl-1(R,S)-methyl-ethyl)amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 86 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-1(R,S)-methyl-ethyl)]-amide: R_f (dichloromethane/methanol=8:2)=0.24; HPLC R_t=10.43/11.16 minutes; FAB-MS $(M+H)^+$=538.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3(R,S)-aminobutyric acid amide hydrochloride.

EXAMPLE 142

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(N-methylcarbamoyl)-1(R,S)-methyl-ethyl]}-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 95 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4- methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(N-methylcarbamoyl)-1(R,S)-methyl-ethyl]}-amide: R_f (dichloromethane/methanol=8:2)=0.33; HPLC R_t=10.78/11.45 minutes; FAB-MS $(M+H)^+$=552.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3(R,S)-amino-N-methylbutyric acid amide hydrochloride.

EXAMPLE 143

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(N,N-dimethylcarbamoyl)-1(R,S)-methyl-ethyl]}-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 95 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(N,N-dimethylcarbamoyl)-1(R,S)-methyl-ethyl]}-amide: R_f (dichloromethane/methanol=8:2)=0.39; HPLC R_t=11.44/12.04 minutes; FAB-MS $(M+H)^+$=566.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3(R,S)-amino-N,N-dimethylbutyric acid amide hydrochloride.

EXAMPLE 144

5-(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-1(R)-isopropylethyl)]-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 71 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-1 (R)-isopropyl-ethyl)]-amide: R_f (dichloromethane/methanol=8:2)=0.27; HPLC R_t=10.64 minutes; FAB-MS $(M+H)^+$=566.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3(S)-amino-4-methyl-pentanoic acid amide hydrochloride.

a) 3(S)-Amino-4-methylpentanoic acid amide hydrochloride is prepared analogously to Example 121 a from 3(R)-benzyloxycarbonylamino-4-methyl-pentanoic acid amide.

b) 3(S)-Benzyloxycarbonylamino-4-methylpentanoic acid amide

2.23 g of 3(S)-benzyloxycarbonylamino-4-methylpentanoic acid ethyl ester and 50 ml of 6N ammonia (in methanol) are stirred for 6 days at 75° C. in a bomb tube. The reaction mixture is concentrated by evaporation and the residue is crystallised from ethyl acetate. The title compound is obtained: R_f (dichloromethane/methanol=95:5)=0.20; m.p. 171°–172° C.

EXAMPLE 145

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(N-methylcarbamoyl)-1 (R)-isopropyl-ethyl]}-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 81 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(N-methylcarbamoyl)-1 (R)-isopropyl-ethyl]amide: R_f (dichloromethane/methanol=8:2)=0.37; HPLC R_t=10.96 minutes; FAB-MS $(M+H)^+$=580.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3(R)-amino-4-methyl-pentanoic acid N-(methyl)amide hydrochloride.

a) 3(R)-Amino-4-methylpentanoic acid N-(methyl)amide hydrochloride is prepared analogously to Example 121

a) from 3(R)-benzyloxycarbonylamino-4-methyl-pentanoic acid N-(methyl)amide.

b) 3(R)-Benzyloxycarbonylamino-4-methylpentanoic acid N-(methyl)amide

2.23 g of 3(R)-benzyloxycarbonylamino-4-methylpentanoic acid ethyl ester and 50 ml of 33% methylamine (in ethanol) are left to stand for 48 hours at room temperature. The reaction mixture is concentrated by evaporation and the residue is crystallised from ethyl acetate. The title compound is obtained: R_f (dichloromethane/methanol=95:5)=0.24; m.p. 190°–191° C.

EXAMPLE 146

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(N,N-dimethylcarbamoyl)1(R)-isopropyl-ethyl]}-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 72 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(N,N-dimethylcarbamoyl)-1 (R)-isopropyl-ethyl]}-amide: R_f (dichloromethane/methanol=8:2)=0.45; HPLC R_t=11.76 minutes; FAB-MS $(M+H)^+$=594.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3(R)-amino-4-methyl-pentanoic acid N,N-dimethylamide hydrochloride.

a) 3(R)-Amino-4-methylpentanoic acid N,N-dimethylamide hydrochloride is prepared analogously to Example 121 a) from 3(R)-benzyloxycarbonylamino-4-methyl-pentanoic acid N,N-dimethylamide.

b) 3(R)-Benzyloxycarbonylamino-4-methylpentanoic acid N,N-dimethylamide

2.23 g of 3(R)-benzyloxycarbonylamino-4-methylpentanoic acid ethyl ester and 50 ml of 30% dimethylamine (in methanol) are stirred for 6 days at 75° C. in a bomb tube. The reaction mixture is concentrated by evaporation and the residue is purified by FC (dichloromethane/methanol=97:3). The title compound is obtained: R_f (dichloromethane/methanol=95:5)=0.40.

EXAMPLE 147

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1(S)-carbamoyl-2-hydroxy-ethyl)]-amide hydrochloride

The title compound is obtained analogously to Example 130 starting from 82 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1(S)-carbamoyl-2-hydroxy-ethyl)]-amide: R_f (dichloromethane/methanol=8:2)=0.16; HPLC R_t=10.09 minutes; FAB-MS $(M+H)^+$=540.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and L-serine amide hydrochloride.

EXAMPLE 148

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1(S),2-dicarbamoyl-ethyl]-amide hydrochloride

The title compound is obtained analogously to Example 130 starting from 68 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1(S),2-dicarbamoyl-ethyl)]-amide: R_f (dichloromethane/methanol=8:2)=0.12; HPLC R_t=9.54 minutes; FAB-MS $(M+H)^+$=567.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and L-aspartic acid diamide hydrochloride.

EXAMPLE 149

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1(S),3-dicarbamoylpropyl)]-amide hydrochloride

The title compound is obtained analogously to Example 130 starting from 83 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1(S),3-dicarbamoylpropyl)]-amide: R_f (dichloromethane/methanol=8:2)=0.13; HPLC R_t=9.50 minutes; FAB-MS $(M+H)^+$=581.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and L-glutaric acid diamide hydrochloride.

EXAMPLE 150

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1(S)-carbamoylpropyl)]-amide hydrochloride

The title compound is obtained analogously to Example 130 starting from 90 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1(S)-carbamoylpropyl)]-amide: R_f (dichloromethane/methanol=8:2)=0.30; HPLC R_t=10.73 minutes; FAB-MS $(M+H)^+$=538.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 2(S)-aminobutyric acid amide hydrochloride.

EXAMPLE 151

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1(S)-carbamoyl-2(S)-methyl-butyl)]-amide hydrochloride

The title compound is obtained analogously to Example 130 starting from 73 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1(S)-carbamoyl-2(S)-methyl-butyl)]-amide: R_f (dichloromethane/methanol=8:2)=0.36; HPLC R_t=11.59 minutes; FAB-MS $(M+H)^+$=566.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and L-isoleucine amide hydrochloride.

EXAMPLE 152

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2(R,S)-carbamoyl-2(R,S)-methyl-ethyl]-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 93 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2(R,S)-carbamoyl-2(R,S)-methyl-ethyl]-amide: R_f (dichloromethane/methanol=8:2)=0.28; HPLC R_t=10.19/10.31 minutes; FAB-MS $(M+H)^+$=538.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3-amino-2(R,S)-methylpropionic acid amide hydrochloride.

EXAMPLE 153

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2(R,S)-(N-methylcarbamoyl)-2(R,S)-methyl-ethyl]-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 93 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-3-methoxypropyloxy)-phenyl]-octanoic acid N-[2(R,S)-(N-methylcarbamoyl)-2(R,S)-methyl-ethyl]amide: R_f (dichloromethane/methanol=8:2)=0.31; HPLC R_t=10.76/10.85 minutes; FAB-MS $(M+H)^+$=552.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3-amino-2(R,S)-methylpropionic acid N-methylamide hydrochloride.

a) 3-Amino-2(R,S)-methylpropionic acid N-methylamide hydrochloride is prepared analogously to Example 121 a) from 3-benzyloxycarbonylamino-2(R,S)-methylpropionic acid N-methylamide.

b) 3-Benzyloxycarbonylamino-2(R,S)-methylpropionic acid N-methylamide

2.52 g of 3-benzyloxycarbonylamino-2(R,S)-methylpropionic acid methyl ester and 50 ml of 33% methylamine (in ethanol) are stirred at room temperature for 48 hours. The reaction mixture is concentrated by evaporation and the title compound is obtained from the residue by crystallisation from ethyl acetate: R_f (dichloromethane/methanol=95:5)=0.42; m.p. 128°–129° C.

c) 3-Benzyloxycarbonylamino-2(R,S)-methylpropionic acid methyl ester

22.6 g of 3-benzyloxycarbonylamino-2(R,S)-methylpropionic acid are left to stand for 24 hours in 230 ml of methanol with a few drops of concentrated sulfuric acid. The reaction mixture is concentrated by evaporation and the residue is purified by FC (220 g of silica gel, dichloromethane). The title compound is obtained: R_f (dichloromethane/methanol=95:5)=0.60.

d) 3-Benzyloxycarbonylamino-2(R,S)-methylpropionic acid

A solution of 41.7 ml of chloroformic acid benzyl ester (9%) in toluene is added to 25 g of 3-amino-2(R,S)-methylpropionic acid in 533 ml of 1N sodium hydroxide at 0° C. The reaction mixture is then stirred for 30 minutes at 0° C. After the addition of 400 ml of diethyl ether, the aqueous phase is removed and 140 ml of 4N hydrochloric acid are added. The crude title compound is obtained from the organic phase by extraction with diethyl ether: R_f (dichloromethane/methanol=8:2)=0.41.

EXAMPLE 154

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-1(S)-methyl-ethyl)]-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 445 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3 (3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-1(S)-methyl-ethyl)]-amide: R_f (dichloromethane/methanol=8:2)=0.24; HPLC R_t=10.27 minutes; FAB-MS $(M+H)^+$=538.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3(S)-aminobutyric acid amide hydrochloride.

EXAMPLE 155

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-.diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-1 (R)-methyl-ethyl)]-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 110 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-1(R)-methyl-ethyl)]-amide: R_f (dichloromethane/

methanol=8:2)=0.24; HPLC R_t=10.92 minutes; FAB-MS $(M+H)^+$=538.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3(R)-aminobutyric acid amide hydrochloride.

EXAMPLE 156

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2(S)-carbamoyl-2(S)-methyl-ethyl]-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 350 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2(S)-carbamoyl-2(S)-methyl-ethyl]-amide (diastereoisomer A): R_f (dichloromethane/methanol=8:2)=0.19; HPLC R_t=10.50 minutes; FAB-MS $(M+H)^+$=538.

The starting material is prepared as follows:

5(S)-Tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2(S)-carbamoyl-2(S)-methyl-ethyl]-amide (diastereoisomer A) and

5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-4-methoxy-3(3-methoxypropyloxy)-phenyl]-octanoic acid [N-[2(S)-carbamoyl-2(R)-methyl-ethyl]-amide (diastereoisomer B)

40 mg of p-toluenesulfonic acid (monohydrate) are added to 1.29 g of 3-tert-butoxy-carbonyl- 5(S)-{2-[N-(2-carbamoyl-2(R,S)-methyl-ethyl)-carbamoyl]-2(S)-isopropyl-ethyl}- 4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl- 1,3-oxazolidine in 50 ml of methanol at 0° C. The reaction solution is stirred for 18 hours at room temperature. After removal of the solvent by evaporation, 100 ml of saturated sodium hydrogen carbonate solution are added to the residue and extraction is carried out repeatedly with ethyl acetate. The organic extracts are concentrated by evaporation and purified by FC (5 times with 60 g of silica gel, dichloromethane/methanol=9:1). The title compounds are obtained:

Diastereoisomer A: R_f (dichloromethane/methanol=95:5)=0.19.

Diastereoisomer B: R_f (dichloromethane/methanol=95:5)=0.14.

The starting material is prepared analogously to Example 124 b) from 3-tert-butoxy-carbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3-amino-2(R,S)-methylpropionic acid amide hydrochloride.

EXAMPLE 157

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2(R)-carbamoyl-2(R)-methyl-ethyl]-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 370 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3 (3-methoxypropyloxy)-phenyl]-octanoic acid N-[2(R)-carbamoyl-2(R)-methyl-ethyl]-amide diastereoisomer B (Example 156 a)): R_f (dichloromethane/methanol=8:2)=0.19; HPLC R_t=10.39 minutes; FAB-MS $(M+H)^+$=538.

EXAMPLE 158

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2(R)-(N-methylcarbamoyl)-2(R)-methyl-ethyl]}-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 60 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2(R)-(N-methylcarbamoyl)- 2(R)-methyl-ethyl]-amide: R_f (dichloromethane/methanol=8:2)=0.31; HPLC R_t=10.33 minutes; FAB-MS $(M+H)^+$=552.

The starting material is prepared analogously to Example 130 a) from 3-tert-butoxy-carbonyl- 5(S)-{2-[N-(2(R)-(N-methylcarbamoyl)-2(R)-methyl-ethyl)-carbamoyl]- 2(S)-isopropyl-ethyl}- 4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}- 2,2-dimethyl-1,3-oxazolidine.

a) 3-Tert-butoxycarbonyl-5(S)-{2(S)-[N-(2(R)-(N-methylcarbamoyl)-2(R)-methyl-ethyl)-carbamoyl]- 2(S)-isopropyl-ethyl}-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-propyl}- 2,2-dimethyl-1,3-oxazolidine

120 mg of 3-tert-butoxycarbonyl-5(S)-{2(S)-[N-(2(R)-methoxycarbonyl)- 2(R)-methyl-ethyl)-carbamoyl]- 2(S)-isopropyl-ethyl}-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine are left to stand for 48 hours at room temperature in 5 ml of 33% methylamine solution (in ethanol). The reaction mixture is concentrated by evaporation and the residue is purified by FC (30 g of silica gel, dichloromethane/methanol=95:5). The title compound is obtained: R_f (dichloromethane/methanol=95:5)=0.30.

b) 3-Tert-butoxycarbonyl-5(S)-{2(S)-[N-(2(R)-methoxycarbonyl)-2(R)-methyl-ethyl)-carbamoyl]- 2(S)-isopropyl-ethyl}-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-propyl- 2,2-dimethyl-1,3-oxazolidine

The title compound is prepared analogously to Example 124 b) from 3-tert-butoxy-carbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}- 2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3-amino-2(R)-methylpropionic acid methyl ester hydrochloride.

c) 3-Amino-2(R)-methylpropionic acid methyl ester hydrochloride

2.7 g of 3-azido-2(R)-methylpropionic acid methyl ester are hydrogenated in the presence of 1.4 g of 10% Pd/C in 50 ml of tetrahydrofuran for 4 hours at room temperature at pH 6.0 (pH-stat; 2N hydrochloric acid). The reaction mixture is filtered and concentrated by evaporation. The title compound is obtained by crystallisation from isopropanol/diethyl ether: ^{1}H NMR (DMSO-d_6), δ(ppm)=7.95(3H, bs), 3.65(3H, s), 3.12–2.78 (3H, m), 1.15 (3H, d); m.p. 122°–125° C.

EXAMPLE 159

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2(S)-(N-methylcarbamoyl)-2(S)-methyl-ethyl]}-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 81 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2(S)-(N-methylcarbamoyl)-2(S)-methyl-ethyl]}-amide: R_f (dichloromethane/methanol=8:2)=0.31;HPLC R_t=10.50 minutes; FAB-MS $(M+H)^+$=552.

The starting material is prepared analogously to Example 158 a) to c) from 3-tert-butoxy-carbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3-amino-2(S)-methylpropionic acid methyl ester hydrochloride.

EXAMPLE 160

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carboxy-2,2-dimethyl-ethyl)]-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 71 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carboxy-2,2-dimethyl-ethyl)]-amide: R_f (dichloromethane/methanol=8:2)=0.52; HPLC R_t=10.95 minutes; FAB-MS $(M+H)^+$=553.

The starting material is prepared analogously to Example 130 a) from 3-tert-butoxy- carbonyl- 5(S)-{2(S)-[N-(2-carboxy-2,2-dimethyl-ethyl)-carbamoyl]-2(S)-isopropyl-ethyl}- 4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl- 1,3-oxazolidine.

a) 3-Tert-butoxycarbonyl-5(S)-{2(S)-[N-(2-carboxy-2,2-dimethyl-ethyl)-carbamoyl]- 2(S)-isopropyl-ethyl}-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}- 2,2-dimethyl-1,3-oxazolidine

36 mg of 3-tert-butoxycarbonyl-5(S)-{2(S)-[N-(2-ethyloxycarbonyl- 2,2-dimethyl-ethyl)-carbamoyl]- 2(S)-isopropyl-ethyl}-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-propyl}- 2,2-dimethyl-1,3-oxazolidine are stirred for 24 hours at room temperature in 1 ml of ethanol and 0.1 ml of 2N potassium hydroxide. The reaction mixture is concentrated by evaporation and, after the addition of 0.1 ml of 2N hydrochloric acid, extracted repeatedly with diethyl ether. The extracts are concentrated by evaporation and purified by FC (18 g of silica gel, dichloromethane/methanol=9:1). The title compound is obtained: R_f (dichloromethane/methanol=9:1)=0.45.

The starting material is prepared analogously to Example 124 b) from 3-tert-butoxy-carbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3-amino-2,2-dimethylpropionic acid ethyl ester.

EXAMPLE 161

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carboxy-2,2-diethyl-ethyl)]-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 136 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carboxy-2,2-diethyl-ethyl)]-amide: R_f (dichloromethane/methanol=8:2)=0.26; HPLC R_t=12.53 minutes; FAB-MS $(M+H)^+$=581.

The starting material is prepared analogously to Example 130 a) from 3-tert-butoxy-carbonyl- 5(S)-{2(S)-[N-(2-carboxy-2,2-diethyl-ethyl)-carbamoyl]-2(S)-isopropyl-ethyl}-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl- 1,3-oxazolidine.

a) 3-Tert-butoxycarbonyl-5(S)-{2-N-(2-carboxy-2,2-diethyl-ethyl)-carbamoyl]- 2(S)-isopropyl-ethyl}- 4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]- propyl}- 2,2-dimethyl-1,3-oxazolidine

258 mg of 3-tert-butoxycarbonyl-5(S)-{2-[N-(2-(2-ethyloxycarbonyl- 2,2-diethyl-ethyl)-carbamoyl]- 2(S)-isopropyl-ethyl}-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine are stirred for 24 hours at 80° C. in 6 ml of ethanol and 0.69 ml of 2N potassium hydroxide. The reaction mixture is concentrated by evaporation and, after the addition of 0.69 ml of 2N hydrochloric acid, extracted repeatedly with diethyl ether. The extracts are concentrated by evaporation and purified by FC (35 g of silica gel, dichloromethane/methanol=9:1). The title compound is obtained: R_f (dichloromethane/methanol=9:1)=0.50.

The starting material is prepared analogously to Example 124 b) from 3-tert-butoxy-carbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3-amino-2,2-diethylpropionic acid ethyl ester.

EXAMPLE 162

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[(1-carboxy-cyclopentyl)-methyl]-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 142 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[(1-carboxy-cyclopentyl)-methyl]-amide: R_f (dichloromethane/methanol=8:2)=0.26; HPLC R_t=12.18 minutes; FAB-MS $(M+H)^+$=579.

The starting material is prepared analogously to Examples 130 a), 161 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 1-(aminomethyl)cyclopentane-1-carboxylic acid ethyl ester.

EXAMPLE 163

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(1H-tetrazol-5-yl)-ethyl]}-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 100 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(1H-tetrazol-5-yl)-ethyl]}-amide: R_f (dichloromethane/methanol=8:2)=0.19; HPLC R_t=12.30 minutes; FAB-MS $(M+H)^+$=549.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 2-(1H-tetrazol-5-yl)-ethylamine.

EXAMPLE 164

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[1(S)-(5-oxopyrrolidin-2-yl)methyl]-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 100 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S)-7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[(1-carboxy-cyclopentyl)-methyl]-amide: R_f (dichloromethane/methanol=8:2)=0.27; HPLC R_t=12.55 minutes; FAB-MS $(M+H)^+$=550.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 5(S)-(aminomethyl)-2-pyrrolidone.

EXAMPLE 165

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[1(R)-(5-oxopyrrolidin-2-yl)methyl]-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 95 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[1 (R)-(5-oxopyrrolidin-2-yl)methyl]-amide: R_f (dichloromethane/methanol=8:2)=0.31; HPLC R_t=12.24 minutes; FAB-MS $(M+H)^+$=550.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 5(R)-(aminomethyl)-2-pyrrolidone.

EXAMPLE 166

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[(N,N-dimethyl)-carbamoylmethyl]}-amide hydrochloride

The title compound is obtained analogously to Example 130 starting from 56 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[(N,N-dimethyl)-carbamoylmethyl]}-amide and after lyophilisation: R_f (ethyl acetate/methanol/conc. ammonia=80: 15:5)=0.42; HPLC R_t=11.82 minutes; FAB-MS $(M+H)^+$=538.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 2(S)-aminoacetic acid (N,N-dimethyl)-amide hydrochloride.

EXAMPLE 167

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[N-(morpholin-4-yl)carbamoylmethyl]amide hydrochloride

The title compound is obtained analogously to Example 130 starting from 76 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[N-(morpholin-4-yl)carbamoylmethyl]-amide and after lyophilisation: R_f (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.43; HPLC R_t=10.66 minutes; FAB-MS $(M+H)^+$=580.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 2-aminoacetic acid N-(morpholin-4-yl)amide hydrochloride.

EXAMPLE 168

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1(S)-carbamoyl-ethyl)]-amide hydrochloride

The title compound is obtained analogously to Example 130 starting from 64 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1(S)-carbamoylethyl)]-amide and after lyophilisation: R_f (ethyl acetate/methanol/conc. ammonia=80: 15:5)=0.42; HPLC R_t=10.48 minutes; FAB-MS $(M+H)^+$=524.

The starting material is prepared analogously to Examples 130 a) and 130 b) from 3-tert-butoxycarbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 2(S)-aminopropionic acid amide hydrochloride.

EXAMPLE 169

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-{1(S)-[(N-methyl)-carbamoyl]-ethyl}-amide hydrochloride

The title compound is obtained analogously to Example 130 starting from 31 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-{1(S)-[(N-methyl)-carbamoyl]-ethyl}-amide and after lyophilisation: R_f (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.38; HPLC R_t=11.08 minutes; FAB-MS. $(M+H)^+$=538.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 2(S)-aminopropionic acid (N-methyl)-amide hydrochloride.

EXAMPLE 170

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-{1(S)-[(N,N-dimethyl)-carbamoyl]-ethyl}-amide hydrochloride

The title compound is obtained analogously to Example 130 starting from 86 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-{1(S)-[(N,N-dimethyl)-carbamoyl]-ethyl}-amide and after lyophilisation: R_f (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.50; HPLC R_t=11.53 minutes; FAB-MS $(M+H)^+$=552.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 2(S)-aminopropionic acid (N,N-dimethyl)-amide hydrochloride.

EXAMPLE 171

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-{1(S)-N-[(morpholin-4-yl)-carbamoyl]-ethyl}amide hydrochloride

The title compound is obtained analogously to Example 130 starting from 51 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-{1(S)-N-[(morpholin-4-yl)-carbamoyl]-ethyl}amide and after lyophilisation: R_f (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.51; HPLC R_t=11.29 minutes; FAB-MS $(M+H)^+$=594.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 2(S)-aminopropionic acid N-(morpholin-4-yl)amide hydrochloride.

EXAMPLE 172

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[1(S)-carbamoyl-butyl]amide hydrochloride

The title compound is obtained analogously to Example 130 starting from 49 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[1(S)-carbamoylbutyl]amide and after lyophilisation: R_f (ethyl acetate)=0.38; HPLC R_t=10.67 minutes; FAB-MS $(M+H)^+$=552.

The starting material is prepared analogously to Example 130 a) and 130 b) from 3-tert-butoxycarbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 2(S)-aminopentanoic acid amide hydrochloride.

EXAMPLE 173

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[1(S)-carbamoyl-2-methyl-propyl]-amide hydrochloride

The title compound is obtained analogously to Example 130 starting from 65 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[1(S)-carbamoyl-2-methyl-propyl]-amide and after lyophilisation: R_f (ethyl acetate/methanol/conc. ammonia=80: 15:5)=0.47; HPLC R_t=11.22 minutes; FAB-MS $(M+H)^+$=552.

The starting material is prepared analogously to Example 130 a) and 130 b) from 3-tert-butoxycarbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 2(S)-amino-3-methylbutyric acid amide hydrochloride.

EXAMPLE 174

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy,.3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[1(S):(N-methylcarbamoyl)-2-methyl-propyl]amide hydrochloride

The title compound is obtained analogously to Example 130 starting from 58 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[1(S)-(N-methylcarbamoyl)-2-methyl-propyl]amide and after lyophilisation: R_f (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.51; HPLC R_t=11.87 minutes; FAB-MS $(M+H)^+$=566.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 2(S)-amino-3-methylbutyric acid (N-methyl)amide hydrochloride.

EXAMPLE 175

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[1(S)-(N,N-dimethylcarbamoyl)-2-methyl-propyl]amide hydrochloride

The title compound is obtained analogously to Example 130 starting from 80 mg of 5(S)-tert-butoxy carbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[1(S)-(N,N-dimethylcarbamoyl)- 2-methyl-propyl]amide and after lyophilisation: R_f (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.62; HPLC R_t=12.36 minutes; FAB-MS $(M+H)^+$=580.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 2(S)-amino-3-methylbutyric acid (N,N-dimethyl)amide hydrochloride.

The starting material is prepared as follows:

a) 2(S)-Amino-3-methylbutyric acid (N,N-dimethyl)amide hydrochloride

0.85 g of 2(S)-tert-butoxycarbonylamino-3-methylbutanoic acid (N,N-dimethyl)amide is dissolved in 10 ml of 4N hydrochloric acid in dioxane at 0° C. and stirred for 7 hours at 0° C. The reaction mixture is lyophilised and the title compound is obtained: R_f (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.23.

EXAMPLE 176

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-.3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-{1(S)-[N-(morpholin-4-yl)carbamoyl]-2-methyl-propyl}amide hydrochloride

The title compound is obtained analogously to Example 130 starting from 74 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-{1(S)-[N-(morpholin-4-yl)carbamoyl]- 2-methyl-propyl}amide and after lyophilisation: R_f (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.59; HPLC R_t=11.81 minutes; FAB-MS $(M+H)^+$=622.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 2(S)-amino-3-methylbutanoic acid N-(morpholin-4-yl)amide hydrochloride.

EXAMPLE 177

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(N-methylsulfonyl)ethyl]amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 90 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(N-methylsulfonyl)ethyl]amide and after lyophilisation: R_f (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.52; HPLC R_t=11.50 minutes; FAB-MS $(M+H)^+$=574.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 2-aminoethyl-(N-methyl)-sulfonamide.

EXAMPLE 178

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-{2-[N-(morpholin-4-yl)-sulfonyl]ethyl}-amide hydrochloride

The title compound is obtained analogously to Example 130 starting from 98 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-{2-[N-(morpholin-4-yl)-sulfonyl]ethyl}-amide and after lyophilisation: R_f (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.53; HPLC R_t=11.63 minutes; FAB-MS $(M+H)^+$=630.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 2-aminoethyl-N-(morpholin-4-yl)-sulfonamide.

The starting material is prepared as follows:

a) 2-Aminoethyl-N-(morpholin-4-yl)-sulfonamide

3.0 g of 2-phthaloylaminoethyl-N-(morpholin-4-yl)-sulfonamide in 20 ml of methanol are stirred for 2 hours under reflux with 20 ml of hydrazine hydrate. The reaction mixture is cooled and 1.0 ml of concentrated hydrochloric acid and 15 ml of methanol are added. The reaction mixture is filtered and the filtrate is concentrated. After the addition of 10 ml of 10% potassium hydroxide solution the title compound is obtained by extraction with dichloromethane: R_f (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.26.

b) 2-Phthaloylaminocthyl-N-(morpholin-4-yl)-sulfonamide

4.77 ml of morpholine are added to 5.0 g of 2-phthaloylaminoethylsulfonyl chloride in 40 ml of dichloromethane at −12° C. The reaction mixture is stirred for 30 minutes at 0° and washed with water. The organic phase is dried over sodium sulfate and concentrated. The title compound is obtained: R_f (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.68.

EXAMPLE 179

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-.[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(N-acetyl)-piperidin-4-yl)ethyl]amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 42 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(N-acetyl)-piperidin-4-yl)ethyl]amide and after lyophilisation: R_f (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.51;

HPLC R_f=12.06 minutes; FAB-MS $(M+H)^+$=606.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 4-(2-aminoethyl)-(N-acetyl)-piperidine hydrochloride.

The starting material is prepared as follows:

a) 4-(2-Aminoethyl)-(N-acetyl)-piperidine hydrochloride is prepared analogously to Example 175 a) from 4-(2-tert-butoxycarbonylaminoethyl)-(N-acetyl)-piperidine.

b) N-Acetyl-4-(2-tert-butoxycarbonylaminoethyl)-piperidine

0.5 g of 4-(2-tert-butoxycarbonylaminoethyl)-piperidine and 0.61 ml of triethylamine are dissolved in 5 ml of dichloromethane and, at 0° C., 0.22 ml of acetyl chloride is added. The reaction mixture is stirred at room temperature for 7 hours and then washed with water. The organic phase is concentrated by evaporation and purified by FC (10 g of silica gel, ethyl acetate/methanol=9:1). The title compound is obtained: R_f (ethyl acetate/methanol=9:1)=0.39.

EXAMPLE 180

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[(N-acetyl-piperidin-4-yl)methyl]amide hydrochloride

The title compound is obtained analogously to Example 130 starting from 71 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[(N-acetylpiperidin-4-yl)methyl]amide and after lyophilisation: R_f (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.44; HPLC R_f=12.83 minutes; FAB-MS $(M+H)^+$=629.

The starting material is prepared analogously to Examples 130 a) and 130 b) from 3-tert-butoxycarbonyl- 5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 4-aminomethyl-(N-acetyl)-piperidine hydrochloride.

EXAMPLE 181

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3- (4-methoxybutyl)-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethyl-ethyl)amide hydrochloride

The title compound is obtained analogously to Example 105 starting from 25 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(4-methoxybutyl)-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethyl-ethyl)amide: R_f (dichloromethane/methanol/conc. ammonia=350:50:1)=0.30; HPLC R_f=13.31 minutes; FAB-MS $(M+H)^+$=550.

The starting material is prepared analogously to Example 82 d), 82 e), Example 83 d), Example 83 and Example 105, except that there is used instead of 4-(3-benzyloxy-propyloxy)- 3-(3-methoxypropyloxy)-bromobenzene in Example 82 d), 4-methoxy-3-(4-methoxy-butyl)-bromobenzene, which is prepared as follows:

a) 4-Methoxy-3-(4-methoxybutyl)-bromobenzene

A solution of 50 g of 4-methoxy-3-(4-methoxy-2-butenyl)-bromobenzene in 700 ml of tetrahydrofuran is hydrogenated for 2 hours under normal pressure and at room temperature in the presence of 2.5 g of 5% Pt/C. The reaction mixture is filtered. The filtrate is concentrated by evaporation. The evaporation residue obtained from the filtrate is purified by FC (1.6 kg of silica gel, hexane/ethyl acetate=20:1). Distillation under a high vacuum yields the title compound: R_f (hexane/ethyl acetate=10:1)=0.38; HPLC R_f=19.92 minutes; FAB-MS $(M+H)^+$=273.

b) 4-Methoxy-3-(4-methoxy-2-butenyl)-bromobenzene

1.1 g of 3-methoxypropyltriphenylphosphonium bromide are added to a solution, stirred at 5°, of 110.8 g of sodium bis(trimethylsilyl)amide in 1200 ml of tetrahydrofuran. The reaction mixture is further stirred for 45 minutes at 0° and then a solution of 100 g of 5-bromo-o-anisaldehyde in 1000 ml of tetrahydrofuran is added dropwise thereto. The reaction mixture is stirred for a further 1 hour at 0°. Then, at 0° C., 1 liter of a saturated ammonium chloride solution is added dropwise. After concentration, the residue is extracted 4 times with ethyl acetate. The organic phases are washed with water and saturated sodium chloride solution and concentrated by evaporation. The residue is purified by FC (500 g of silica gel, hexane/ethyl acetate=5:1). Distillation under a high vacuum yields the title compound: R_f (hexane/ethyl acetate=4:1)=0.61.

EXAMPLE 182

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(N,N-dimethylcarbamoyl)ethyl]-amide sodium dihydrogen citrate

768 mg of 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-[2-(N,N-dimethylcarbamoyl)ethyl]amide hydrochloride (Example 134) are stirred in 50 ml of 0.1N sodium hydroxide and extracted repeatedly with dichloromethane. The extracts are concentrated and the residue is dissolved in 50 ml of ethanol. 274 mg of citric acid monohydrate, 50 ml of water and 1.30 ml of 1N sodium hydroxide are added in succession to the stirred solution. The solution is then concentrated to dryness by evaporation and the residue is taken up in 100 ml of water and lyophilised. The lyophilisate is dissolved in methanol and clarified by filtration; the filtrate is concentrated and the residue is dried at room temperature under a high vacuum. The title compound is obtained in the form of a white amorphous solid having a melting point of 80° C.

EXAMPLE 183

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3- (4-methoxybutyl)-phenyl-octanoic acid N-(2-morpholinoethyl)amide dihydrochloride

The title compound is obtained analogously to Example 124 starting from 100 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3 (4-methoxybutyl)-phenyl]-octanoic acid N-[2-(4-morpholino)ethyl]-amide: R_f (dichloromethane/methanol=10:1)=0.21; HPLC R_f=12.69 minutes; FAB-MS $(M+H)^+$=564.

The starting material is prepared as follows:

a) 5(S)-Tert-butoxycarbonylamino-4(S)-hydroxy-2(S), 7(S)-diisopropyl-8-[4-methoxy- 3-(4-methoxybutyl)-phenyl]-octanoic acid N-[2-(4-morpholino)-ethyl]-amide

10 ml of acetic acid are added to a solution of 100 mg of 3(S)-isopropyl-5(S)-{1(S)-tert-butoxycarbonylamino- 3(S)-isopropyl-4-[4-methoxy-3-(4-methoxybutyl)-phenyl]-butyl] -tetrahydrofuran- 2-one (for preparation see Example 181) in 2 ml of 4-(2-aminoethyl)morpholine. The reaction mixture is stirred for 39 hours at 80° C. and then concentrated by evaporation in a rotary evaporator. Purification of the residue by FC (dichloromethane/methanol=10:1) yields the title compound in the form of a crude product. Crystallisation from diethyl ether/hexane yields the title compound: m.p. –94°–96° C., R_f (dichloromethane/methanol=10:1) -0.35; HPLC R_t=17.42 minutes; FAB-MS $(M+H)^+$=664.

EXAMPLE 184

5(S)-Amino-4(S),8(R,S)-dihydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-. 3-(2-methoxymethoxyethyl)-phenyl]-octanoic acid (N-butyl)-amide

40 mg of 5(S)-azido-4(S),8(R,S)-dihydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(2-methoxymethoxyethyl)-phenyl]-octanoic acid (N-butyl)-amide are hydrogenated in 10 ml of methanol/acetic acid (9:1) in the presence of 20 mg of 10% Pd/C at room temperature and under normal pressure. The reaction mixture is filtered and concentrated by evaporation. The residue is purified by FC (2.4 g of silica gel, dichloromethane/methanol=9:1). The title compound is obtained: R_f (dichloromethane/methanol=9:1)=0.17; HPLC R_t=11.44 and 12.63 minutes (diastereoisomeric mixture); FAB-MS (M+H)+= 525.

a) 5(S)-Azido-4(S)-8(R,S)-dihydroxy-2(S)-7(S)-diisopropyl-8-[4-methoxy-3-(2-methoxy-methoxyethyl)-phenyl]-octanoic acid (N-butyl)-amide

A solution of 400 mg of 3(S)-isopropyl-5(S)-{1(S)-azido-4(R,S)-hydroxy-3(S)-isopropyl- 4-[4-methoxy-3-(2-methoxymethoxyethyl)-phenyl]-butyl}-tetrahydrofuran-2-one (Example 81 d) and 3.8 ml of n-butylamine is stirred for 16 hours at 50° C. and then concentrated by evaporation. Purification of the residue by FC (50 g of silica gel, hexane/ethyl acetate=1:1) yields the title compound: R_f (hexane/ethyl acetate=1:1)=0.44; HPLC R_t=16.13 and 17.03 minutes (diastereoisomeric mixture).

EXAMPLE 185

5(S)-Amino-4(S),8(S or R)-dihydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethyl-ethyl)-amide hydrochloride

60 mg of 5(S)-azido-4(S),8(S or R)-dihydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethyl-ethyl)-amide and 6 ml of ethanolamine are hydrogenated in 8 ml of ethanol in the presence of 120 mg of 5% PdO/C for 2 hours at room temperature and under normal pressure. The reaction mixture is filtered and concentrated by evaporation. The residue is dissolved in 0.5 ml of dioxane and 23 ul of 4N hydrochloric acid in dioxane are added. The title compound is obtained after lyophilisation: HPLC R_t=10.74; FAB-MS (M+H)+= 568.

The starting materials are prepared as follows:

a) 5(S)-Azido-4(S),8(S or R)-dihydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethyl-ethyl)-amide

150 mg of 3(S)-isopropyl-5(S)-{1(S)-azido-4(S or R)-hydroxy-3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-tetrahydrofuran-2-one (Example 185b) diastereoisomer B) and 109 mg of 3-amino-2,2-dimethylpropionic acid amide are stirred in 3 ml of triethylamine with 30 mg of 2-hydroxypyridine for 24 hours under reflux temperature. After removal of the solvent by evaporation, the residue, in diethyl ether, is washed repeatedly with water. The organic extracts are concentrated by evaporation and purified by FC (10 g of silica gel, dichloromethane/methanol=95:5). The title compound is obtained: R_f (dichloromethane/methanol=95:5)=0.22; HPLC R_t=14.88 minutes.

b) 3(S)-Isopropyl-5(S)-{1(S)-azido-4(S or R)-hydroxy-3(S)-isopropyl-4-[4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-butyl}-tetrahydrofuran-2-one (A) and

3(S)-isopropyl-5(S)-{1(S)-azido-4(S or R)-hydroxy-3(S)-isopropyl-4-I4-methoxy- 3-(3-methoxypropyloxy)-phenyl]-butyl}-tetrahydrofuran-2-one (B)

Separation of 0.5 g of 3(S)-isopropyl-5(S)-{1(S)-azido-4(R,S)-hydroxy-3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-tetrahydrofuran-2-one (diastereoisomeric mixture) by means of preparative HPLC on Kromasil 7 C18 (EKA-Nobel, A.B. Sweden); mobile phase: A) water B) acetonitrile, gradient: 20 -80% B in 40 minutes. The two pure diastereoisomers A and B are obtained (isomer A is eluted first). After concentration of the eluate fractions by evaporation, the aqueous residue is extracted with ethyl acetate. The organic extracts are dried over magnesium sulfate and concentrated. The title compounds are obtained: diastereoisomer A) HPLC R_t=18.53 minutes and B) HPLC R_t=19.49 minutes.

c) 3(S)-Isopropyl-5(S)-1(S)-azido-4(R,S)-hydroxy-3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-tetrahydrofuran-2-one

45.1 ml of a 1N n-butyllithium solution (in hexane) are added dropwise at –75° C. to a mixture of 12.1 g of 4-methoxy-3-(3-methoxypropyloxy)-bromobenzene and 9.7 ml of 4-methylmorpholine in 75 ml of tetrahydrofuran. The reaction mixture is stirred for a further 20 minutes at –75° C. and then, at from –75° C. to –60° C., a suspension of magnesium bromide in tetrahydrofuran (freshly prepared from 1.6 g of magnesium powder and 5.7 ml of 1,2-dibromoethane in 150 ml of tetrahydrofuran) is added. The reaction mixture is stirred for a further 30 minutes and then, at –75° C., a solution of 8.84 g of 3(S)-isopropyl- 5(S)-[1(S)-azido-3(S)-isopropyl-4-oxobutyl]-tetrahydrofuran-2-one in 75 ml of tetrahydrofuran is added. The reaction mixture is then stirred for 15 minutes at –75° C. and subsequently 70 ml of saturated ammonium chloride solution are added. The reaction mixture is then poured into 180 ml of saturated sodium chloride solution:water (1:1) and extracted with ethyl acetate (2x360 ml). The organic phases are dried over magnesium sulfate and concentrated by evaporation. The title compound is obtained by purifying the residue by FC (240 g of silica gel, ethyl acetate/hexane=1:2): R_f (ethyl acetate/hexane=1:2)=0.16; HPLC R_t=18.53 and 19.49 minutes (diastereoisomeric mixture).

d) 4-Methoxy-3-(3-methoxypropyloxy)-bromobenzene

66.0 g of potassium carbonate and 3-methoxy-1-bromopropane are added at room temperature to a solution of

64.6 g of 5-bromo-2-methoxyphenol in 350 ml of acetonitrile. The reaction mixture is stirred under reflux for 14 hours. After removal of the solvent by evaporation, 1200 ml of ice/water are added to the residue and extraction is carried out with ether. The organic extracts are washed with saturated sodium chloride solution, dried over magnesium sulfate and concentrated by evaporation. Distillation under a high vacuum yields the title compound: R_f (hexane/ethyl acetate=4:1)=0.33; b.p.=126°–129° C./1.4 mbar; HPLC R_t=16.38 minutes; MS (M^+)=274, 276.

EXAMPLE 186

5(S)-Amino-4(S),8(R or S)-dihydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoyl- 2,2-dimethyl-ethyl)-amide hydrochloride

The title compound is obtained analogously to Example 185 starting from 5(S)-azido- 4(S),8(R or S)-dihydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethyl-ethyl)-amide: HPLC R_t=10.68; FAB-MS $(M+H)^+$=568.

The starting material is prepared analogously to Example 185a) from 3(S)-isopropyl- 5(S)-{1(S)-azido-4(R or S)-hydroxy-3(S)-isopropyl-4-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-butyl}-tetrahydrofuran- 2-one (Example 185 b) diastereoisomer A).

EXAMPLE 187

Gelatin solution

A sterile-filtered aqueous solution, containing 20% cyclodextrins as solubiliser, of one of the compounds of formula I mentioned in the preceding Examples as active ingredient, is so mixed, with the application of heat and under aseptic conditions, with a sterile gelatin solution containing phenol as preservative, that 1.0 ml of solution has the following composition:

active ingredient	3 mg
gelatin	150.0 mg
phenol	4.7 mg
dist. water containing 20% cyclodextrins as solubiliser	1.0 ml

EXAMPLE 188

Sterile dry substance for injection

5 mg of one of the compounds of formula I mentioned in the preceding Examples as active ingredient are dissolved in 1 ml of an aqueous solution containing 20 mg of mannitol and 20% cyclodextrins as solubiliser. The solution is sterile-filtered and, under aseptic conditions, introduced into a 2 ml ampoule, deep-frozen and lyophilised. Before being used, the lyophilisate is dissolved in 1 ml of distilled water or 1 ml of physiological saline. The solution is administered intramuscularly or intravenously. The formulation can also be filled into double-chamber disposable syringes.

EXAMPLE 189

Nasal spray

500 mg of finely ground (<5.0 gm) powder of one of the compounds of formula I mentioned in the preceding Examples are suspended as active ingredient in a mixture of 3.5 ml of "Myglyol 8 12" and 0.08 g of benzyl alcohol. The suspension is introduced into a container having a metering valve. 5.0 g of "Freon 12" are introduced under pressure through the valve into the container. The "Freon" is dissolved in the Myglyol/benzyl alcohol mixture by shaking. The spray container contains approximately 100 single doses which can be administered individually.

EXAMPLE 190

Film-coated tablets

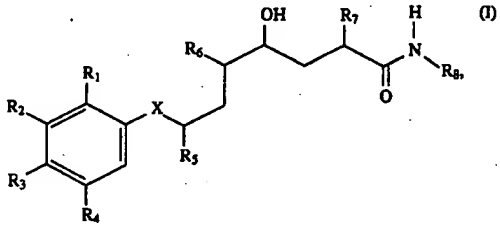
The following constituents are processed for the preparation of 10 000 tablets each containing 100 mg of active ingredient:

active ingredient	1000 g
corn starch	680 g
colloidal silicic acid	200 g
magnesium stearate	20 g
stearic acid	50 g
sodium carboxymethyl starch	250 g
water	quantum satis

A mixture of one of the compounds of formula I mentioned in the preceding Examples as active ingredient, 50 g of corn starch and the colloidal silicic acid is processed into a moist mass with starch paste prepared from 250 g of corn starch and 2.2 kg of demineralised water. The mass is forced through a sieve having a mesh size of 3 mm and dried at 45° for 30 minutes in a fluidised bed drier. The dried granules are pressed through a sieve having a mesh size of 1 ram, mixed with a previously sieved mixture (1 mm sieve) of 330 g of corn starch, the magnesium stearate, the stearic acid and the sodium carboxymethyl starch, and compressed to form slightly biconvex tablets.

What is claimed is:

1. A novel δ-amino-γ-hydroxy-ω-aryl-alkanoic acid amide of formula I



(I)

wherein

R_1 is hydrogen, hydroxy, lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy or free or esterified or amidated carboxy-lower alkoxy.

R_2 is hydrogen, lower alkyl, cycloalkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, hydroxy, optionally lower alkanoylated, halogenated or sulfonylated hydroxy-lower alkoxy; amino-lower alkyl that is unsubstituted or substituted by lower alkyl, by lower alkanoyl and/or by lower alkoxycarbonyl; optionally hydrogenated het-

eroaryl-lower alkyl; amino-lower alkoxy that is substituted by lower alkyl, by lower alkanoyl and/or by lower alkoxycarbonyl; oxo-lower alkoxy, lower alkoxy, cycloalkoxy, lower alkenyloxy, cycloalkoxy-lower alkoxy, lower alkoxy-lower alkoxy, lower alkoxy-lower alkenyl, lower alkenyloxy-lower alkoxy, lower alkoxy-lower alkenyloxy, lower alkenyloxy-lower alkyl, lower alkanoyl-lower alkoxy, optionally S-oxidised lower alkylthio-lower alkoxy, lower alkylthio-(hydroxy)-lower alkoxy, aryl-lower alkoxy, optionally hydrogenated heteroaryl-lower alkoxy, cyano-lower alkoxy, free or esterified or amidated carboxy-lower alkoxy or free or esterified or amidated carboxy-lower alkyl.

R_3 is optionally halogenated lower alkyl, lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, hydroxy-lower alkyl, optionally S-oxidised lower alkylthio-lower alkyl, optionally hydrogenated heteroarylthio-lower alkyl, optionally hydrogenated heteroaryl-lower alkyl; amino-lower alkyl that is unsubstituted or N-mono- or N,N-di-lower alkylated. N-lower alkanoylated or N-lower alkane-sulfonylated or N,N-disubstituted by lower alkylene, by unsubstituted or N'-lower alkylated or N'-lower alkanoylated aza-lower alkylene, by oxa-lower alkylene or by optionally S-oxidised thia-lower alkylene; cyano-lower alkyl, free or esterified or amidated carboxy-lower alkyl, cycloalkyl, aryl, hydroxy, lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy, cycloalkoxy-lower alkoxy, hydroxy-lower alkoxy, aryl-lower alkoxy, optionally halogenated lower alkoxy, optionally S-oxidised lower alkylthio-lower alkoxy, optionally hydrogenated heteroaryl-lower alkoxy, optionally hydrogenated heteroarylthio-lower alkoxy; amino-lower alkoxy that is unsubstituted or N-mono- or N,N-di-lower alkylated. N-lower alkanoylated or N-lower alkanesulfonylated or substituted by lower alkylene, by unsubstituted or N'-lower alkylated or N'-lower alkanoylated aza-lower alkylene, by oxa-lower alkylene or by optionally S-oxidised thia-lower alkylene; cyano-lower alkoxy or free or esterified or amidated carboxy-lower alkoxy,

R_4 is hydrogen, lower alkyl, hydroxy, lower alkoxy or cycloalkoxy.

X is methylene,

R_5 is lower alkyl or cycloalkyl.

R_6 is unsubstituted or N-mono- or N,N-di-lower alkylated or N-lower alkanoylated amino,

R_7 is lower alkyl, lower alkenyl, cycloalkyl or aryl-lower alkyl, and

R_8 is lower alkyl, cycloalkyl, free or aliphatically esterified or etherified hydroxy-lower alkyl; amino-lower alkyl that is unsubstituted or N-lower alkanoylated or N-mono- or N,N-di-lower alkylated or N,N-disubstituted by lower alkylene, by hydroxy-. lower alkoxy- or lower alkanoyloxy-lower alkylene, by unsubstituted or N'-lower alkanoylated or N'-lower alkylated aza-lower alkylene, by oxa-lower alkylene or by optionally S-oxidised thia-lower alkylene; free or esterified or amidated carboxy-lower alkyl, free or esterified or amidated dicarboxy-lower alkyl, free or esterified or amidated carboxy-(hydroxy)-lower alkyl, free or esterified or amidated carboxycycloalkyl-lower alkyl, cyano-lower alkyl, lower alkanesulfonyl-lower alkyl, unsubstituted or N-mono- or N,N-di-lower alkylated thiocarbamoyl-lower alkyl, unsubstituted or N-mono- or N,N-di-lower alkylated sulfamoyl-lower alkyl, or a heteroaryl radical bonded via a carbon atom and optionally hydrogenated and/or oxo-substituted, or lower alkyl substituted by a heteroaryl radical bonded via a carbon atom and optionally hydrogenated and/or oxo-substituted,

or a salt thereof.

2. A compound according to claim 1 of formula I wherein

R_1 is hydrogen, hydroxy, lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy, carboxy-lower alkoxy, lower alkoxycarbonyl-lower alkoxy, carbamoyl-lower alkoxy or N-mono- or N,N-di-lower alkylcarbamoyl-lower alkoxy.

R_2 is hydrogen, lower alkyl, cycloalkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, hydroxy, lower alkanoyloxy-lower alkyl, hydroxy-lower alkoxy, halo-(hydroxy)-lower alkoxy, lower alkane-sulfonyl-(hydroxy)-lower alkoxy, amino-lower alkyl, lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl, lower alkanoylamino-lower alkyl, lower alkoxycarbonylamino-lower alkyl, amino-lower alkoxy, lower alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy, lower alkanoylamino-lower alkoxy, lower alkoxycarbonylamino-lower alkoxy, oxo-lower alkoxy, lower alkoxy, cycloalkoxy, lower alkenyloxy, cycloalkoxy-lower alkoxy, lower alkoxy-lower alkoxy, lower alkoxy-lower alkenyl, lower alkenyloxy-lower alkoxy, lower alkoxy-lower alkenyloxy, lower alkenyloxy-lower alkyl, lower alkanoyl-lower alkoxy, lower alkylthio-lower alkoxy, lower alkanesulfonyl-lower alkoxy, lower alkylthio-(hydroxy)-lower alkoxy, aryl-lower alkoxy, thiazolylthio-lower alkoxy or thiazolinylthio-lower alkoxy, imidazolylthio-lower alkoxy, optionally N-oxidised pyridylthio-lower alkoxy, pyrimidinylthio-lower alkoxy, cyano-lower alkoxy, lower alkoxycarbonyi-lower alkoxy, carbamoyl-lower alkoxy, N-mono- or N, N-all-lower alkylcarbamoyl-lower alkoxy, carboxy-lower alkyl, lower alkoxy-carbonyl-lower alkyl, carbamoyl-lower alkyl or N-mono- or N,N-di-lower alkyl-carbamoyl-lower alkyl,

R_3 is lower alkyl, polyhalo-lower alkyl, lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, hydroxy-lower alkyl, lower alkylthio-lower alkyl, lower alkanesulfonyl-lower alkyl, optionally partially hydrogenated or N-oxidised pyridyl-lower alkyl, thiazolylthio-lower alkyl or thiazolinylthio-lower alkyl, imidazolylthio-lower alkyl, optionally N-oxidised pyridylthio-lower alkyl, pyrimidinylthio-lower alkyl, amine-lower alkyl, lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl, lower alkanoylamino-lower alkyl, lower alkanesulfonylamino-lower alkyl, polyhalo-lower alkanesulfonylamino-lower alkyl, pyrrolidino-lower alkyl, piperidino-lower alkyl, piperazino-, N'-lower alkylpiperazino- or N'-lower alkanoylpiperazino-lower alkyl, morpholino-lower alkyl, thiomorpholino-. S-oxothiomorpholino- or S,S-dioxothiomorpholino-lower alkyl, cyano-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, carbamoyl-lower alkyl, N-mono- or N,N-di-lower alkylcarbamoyl-lower alkyl, cycloalkyl; phenyl or naphthyl that is unsubstituted or mono-. di- or tri-substituted by lower alkyl, lower alkoxy, hydroxy, lower alkylamino, di-lower alkylamino, halogen and/or by trifluoromethyl; hydroxy, lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy, cycloalkoxy-lower alkoxy, hydroxy-lower alkoxy; phenyl-lower alkoxy or naphthyl-lower alkoxy that is unsubstituted or mono-, di- or tri-substituted by lower alkyl, lower alkoxy, hydroxy, lower

alkylamino, di-lower alkylamino, halogen and/or by trifluoromethyl; lower alkoxy, polyhalo-lower alkoxy, lower alkylthio-lower alkoxy, lower alkanesulfonyl-lower alkoxy, optionally hydrogenated heteroaryl-lower alkoxy, optionally partially or fully hydrogenated hetero-arylthio-lower alkoxy, such as thiazolylthio-lower alkoxy or thiazolinylthio-lower alkoxy, imidazolylthio-lower alkoxy, optionally N-oxidised pyridylthio-lower alkoxy, pyrimidinylthio-lower alkoxy, amine-lower alkoxy, lower alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy, lower alkanoylamino-lower alkoxy, lower alkanesulfonylamino-lower alkoxy, polyhalo-lower alkanesulfonylamino-lower alkoxy, pyrrolidino-lower alkoxy, piperidino-lower alkoxy, piperazino-, N'-lower alkylpiperazino- or N'-lower alkanoylpiperazino-lower alkoxy, morpholino-lower alkoxy, thiomorpholino-, S-oxothiomorpholino-or S,S-dioxothiomorpholino-lower alkoxy, cyano-lower alkoxy, carboxy-lower alkoxy, lower alkoxycarbonyl-lower alkoxy, carbamoyl-lower alkoxy or N-mono- or N,N-di-lower alkylcarbamoyl-lower alkoxy,

R_4 is hydrogen, lower alkyl, hydroxy, lower alkoxy or cycloalkoxy.

X is methylene,

R_5 is lower alkyl or cycloalkyl.

R_6 is amino, lower alkylamino, di-lower alkylamino or lower alkanoylamino,

R_7 is lower alkyl, lower alkenyl, cycloalkyl, or phenyl- or naphthyl-lower akyl that is unsubstituted or mono-, di- or tri-substituted by lower alkyl, lower alkoxy, hydroxy, lower alkylamino, di-lower alkylamino, halogen and/or by trifluoromethyl, and

R_8 is lower alkyl, cycloalkyl, hydroxy-lower alkyl, lower alkanoyloxy-lower alkyl, lower alkoxy-lower alkyl or lower alkenyloxy-lower alkyl, amino-lower alkyl, lower alkanoylamino-lower alkyl. N-mono- or N,N-di-lower alkylamino-lower alkyl, optionally hydroxylated or lower alkoxylated piperidino-lower alkyl, such as piperidino-lower alkyl, hydroxypiperidino-lower alkyl or lower alkoxy-piperidino-lower alkyl, piperazino-, N'-lower alkylpiperazino- or N'-lower alkanoylpiperazino-lower alkyl, unsubstituted or lower alkylated morpholino-lower alkyl, such as morpholino-lower alkyl or dimethylmorpholino-lower alkyl, or optionally S-oxidised thiomorpholino-lower alkyl, such as thiomorpholino-lower alkyl, S,S-dioxothiomorpholino-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, carbamoyl-lower alkyl, N-mono- or N,N-di-lower alkylcarbamoyl-lower alkyl, dicarboxy-lower alkyl, di-lower alkoxycarbonyl-lower alkyl, dicarbamoyl-lower alkyl, di-(N-mono- or N,N-di-lower alkylcarbamoyl)-lower alkyl, carboxy-(hydroxy)-lower alkyl, lower alkoxy-carbonyl-(hydroxy)-lower alkyl or carbamoyl-(hydroxy)-lower alkyl, cyano-lower alkyl, lower alkanesulfonyl-lower alkyl, sulfamoyl-lower alkyl, lower alkyl-sulfamoyl-lower alkyl, di-lower alkylsulfamoyl-lower alkyl, thiocarbamoyl-lower alkyl, lower alkylthiocarbamoyl-lower alkyl, di-lower alkylthiocarbamoyl-lower alkyl, pyrrolidinyl, imidazolyl, benzimidazolyl, oxadiazolyl, pyridyl, oxopiperidinyl, quinolinyl, unsubstituted or N-lower alkanoylated piperidyl or pyrrolidinyl, imidazolyl-lower alkyl, benzimidazolyl-lower alkyl, oxadiazolyl-lower alkyl, pyridyl-lower alkyl, unsubstituted or N-lower alkanoylated piperidyl-lower alkyl or pyrrolidinyl-lower alkyl, oxopiperidinyl-lower alkyl, quinolinyl-lower alkyl, morpholinocarbonyl-lower alkyl or unsubstituted or N-lower alkanoylated piperidyl-lower alkyl,

or a salt thereof.

3. A compound according to claim 1 of formula I wherein

R_1 is hydrogen,

R_2 is lower alkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkoxy, lower alkoxy-tower alkoxy-lower alkyl; phenyl-lower alkoxy that is unsubstituted or substituted by bower alkyl, lower alkoxy, hydroxy, halogen, nitro and/or by amino; optionally N-oxidised pyridyl-lower alkoxy, lower alkylthio-lower alkoxy, lower alkanesulfonyl-lower alkoxy, lower alkanoyl-lower alkoxy, optionally N-oxidised pyridyl-lower alkoxy, cyano-lower alkoxy, carboxy-lower alkoxy, lower alkoxycarbonyl-lower alkoxy, carbamoyl-lower alkoxy, lower alkylcarbamoyl-lower alkoxy or di-lower alkylcarbamoyl-lower alkoxy,

R_3 is hydrogen, lower alkyl, hydroxy, lower alkoxy or polyhalo-lower alkoxy,

R_4 is hydrogen or together with R_3 is lower alkylidenedioxy,

X is methylene,

R_5 is lower alkyl or cycloalkyl.

R_6 is amine, lower alkylamino, di-lower alkylamino or lower alkanoylamino,

R_7 is lower alkyl, and

R_8 is lower alkyl, hydroxy-lower alkyl, lower alkanoyl-lower alkyl, lower alkoxy-lower alkyl, lower alkenyloxy-lower alkyl, amino-lower alkyl, lower alkanoylamino-lower alkyl, such as 2-(C_1–C_4alkanoylamino)-2-methyl-propyl, such as 2-acetylamino-2-methyl-propyl or 2-formylamino-2-methyl-propyl, N-mono- or N,N-di-lower alkylamino-lower alkyl, piperidino-lower alkyl, hydroxypiperidino-lower alkyl, lower alkoxypiperidino-lower alkyl, morpholino-lower alkyl, dimethylmorpholino-lower alkyl, thiomorpholino-lower alkyl. S,S-dioxothiomorpholino-lower alkyl, Carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, carbamoyl-lower alkyl, N-mono- or N,N-di-lower alkylcarbamoyl-lower alkyl, carboxy-(hydroxy)-lower alkyl, lower alkoxycarbonyl-(hydroxy)-lower alkyl, carbamoyl-(hydroxy)-lower alkyl, 5- or 6-membered carboxycycloalkyl-lower alkyl, 5- or 6-membered lower alkoxycarbonylcycloalkyl-lower alkyl. 5- or 6-membered carbamoylcycloalkyl-lower alkyl, 5- or 6-membered N-mono- or N, N-di-lower alkylcarbamoylcycloalkyl-lower alkyl, cyano-lower alkyl, lower alkanesulfonyl-lower alkyl, sulfamoyl-lower alkyl, lower alkylsulfamoyl-lower alkyl or di-lower alkylsulfamoyl-lower alkyl, imidazolyl-lower alkyl, oxopyrrolidinyl-lower alkyl, benzimidazolyl-lower alkyl, oxadiazolyl-lower alkyl, pyridyl-lower alkyl, oxopiperidinyl-lower alkyl or quinolinyl-lower alkyl, piperidin-4-yl-lower alkyl or 1-C_1–C_7-lower alkanoylpiperidin-4-yl-lower alkyl,

or a salt thereof.

4. A compound according to claim I of formula I wherein

R_1 and R4 are hydrogen.

R_2 is C_1–C_4alkoxy-C_1–C_4alkoxy or C_1–C_4alkoxy-C_1–C_4alkyl,

R_3 is C_1–C_4alkyl or C_1–C_4alkoxy,

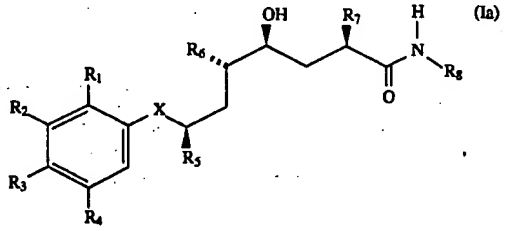
R_6 is amino,

X is methylene,

R_5 and R7 are branched C_1–C_4alkyl, and

R_8 is carbamoyl-C_1–C_4alkyl, N-C_1–C_4alkylcarbamoyl-C_1–C_4alkyl, N,N-di-C_1–C_4alkyl-carbamoyl-C_1–C_4alkyl, morpholino-C_1–C_4alkyl, thiomorpholino-C_1–C_4alkyl, 4-(1-C $_1$–C_4alkanoylpiperidyl)-C_1–C_4alkyl or 2-oxopyrrolidinyl-C_1–C_4alkyl, or a salt thereof.

5. A compound according to claim 1 of formula I wherein at least one asymmetric carbon atom of the main chain has the stereochemical configuration shown in formula Ia



(Ia)

each of the variables being as defined in claim 1, or a pharmaceutically acceptable salt thereof.

6. A compound according to claim 1 selected from the group consisting of 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(p-tert-butyl-phenyl)-octanoic acid (N-butyl)amide;

2(R, S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-ethyl-8-(p-tert-butyl-phenyl)-octanoic acid (N-butyl)amide;

2(R, S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-methyl-8-(4-biphenyl-octanoic acid (N-butyl)amide;

2(R)-methyl-4(S)-hydroxy-5(S)-amine-7(S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide;

2(R, S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(2-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide;

2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-ethoxycarbonylmethoxy- 4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide;

2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-allyloxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide;

2(R, S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-methoxycarbonyl-allyloxy- 4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide;

2(R, S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-methoxycarbonyl-methoxy- 4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide;

2(R, S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-carbamoyl-methoxy- 4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide;

2(R, S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(pyrid-2-yl-methoxy)- 4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide;

2(R, S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(pyrid-4-yl-methoxy)- 4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide;

2(R, S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(N-oxido-pyrid-2-yl-methoxy)- 4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide;

2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2-ethoxycarbonylallyl-oxy)- 4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide;

2(R. S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2-ethoxycarbonyl-propyloxy)- 4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide;

2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(methylthio-methoxy)- 4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide;

2(R, S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(methylsulfonyl-methoxy)- 4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide;

2(R, S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(carboxy-methoxy)- 4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide;

2(R, S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3,3-dimethyl- 2-oxo-butyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide;

2(R, S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2-nitrobenzyloxy) 4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide;

2(R, S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2-aminobenzyloxy)- 4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide;

2(R, S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-chloro-2(R hydroxypropyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide;

2(R, S]-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-methylthio- 2(S,R)-hydroxypropyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide;

2(R, S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-methylsulfonyl-(S,R)-hydroxypropyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide;

2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(methylsulfonyl-methoxy)- 4-tert-butyl-phenyl]-octanoic acid (N-3-morpholino-propyl)amide;

2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-methoxycarbonyl-methoxy-phenyl)-octanoic acid (N-butyl)amide;

2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(methoxycarbonyl-methoxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide;

2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(N-methyl-carbamoyl-methoxy)- 4-methoxy-phenyl]-octanoic acid (N-butyl)amide;

2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-methylsulfonyl-propyloxy)- 4-methoxy-phenyl]-octanoic acid (N-butyl)amide;

2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(methylsulfonyl-methoxy)- 4-methoxy-phenyl]-octanoic acid (N-butyl)amide;

2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-methoxy-propyloxy)- 4-methoxy-phenyl]-octanoic acid (N-butyl)amide;

2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2-methoxy-ethoxy)- 4-methoxy-phenyl]-octanoic acid (N-butyl)amide;

2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-hydroxy-propyloxy)- 4-methoxy-phenyl]-octanoic acid (N-butyl)amide;

2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(carbamoyl methoxy)- 4-methoxy-phenyl]-octanoic acid (N-butyl)amide;

2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-cyanomethoxy- 4-methoxy-phenyl)-octanoic acid (N-butyl)amide;

2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(4-methoxy-butoxy)- 4-methoxy-phenyl]-octanoic acid (N-butyl)amide;

2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2-ethoxy-ethoxy)- 4-methoxy-phenyl]-octanoic acid (N-butyl)amide;

2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-{3-[2-(2-methoxy-ethoxy)-ethoxy]- 4-methoxy-phenyl}-octanoic acid (N-butyl)amide;

2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-pentyloxy- 4-methoxy-phenyl)-octanoic acid (N-butyl)amide;

2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-benzyloxy- 4-methoxy-phenyl)-octanoic acid (N-butyl)amide;

2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-ethoxy-propyloxy)-4 methoxy-phenyl]-octanoic acid (N-butyl)amide;

2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(pyrid-4-ylmethoxy)- 4-methoxy-phenyl]-octanoic acid (N-butyl)amide;

2(R, S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(2-ethoxycarbonyl-methoxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide;

2(R, S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(2-cthoxycarbonyl- 4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-(3-hydroxypropyloxy)- 3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-2,2-dimethyl-ethyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-isopropyl-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-2,2-dimethyl-ethyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-tert-butyl-3-(3-methoxy-propyl-oxy)-phenyl]-octanoic acid [N-(2-carbamoyl-2,2-dimethyl-ethyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-(3-methylsulfonyl-propyloxy)- 3-(3-methoxy-propyloxy) -phenyl]-octanoic acid (N-2-morpholinoethyl)amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-(3-methylsulfonyl-propyloxy)- 3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-2,2-dimethyl-ethyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[3,4-di(3-hydroxypropyloxy)-phenyl]-octanoic acid (N-2-morpholinoethyl)amide;

5(S)-amino-4(S)-hydroxy-2(S). 7(S)-diisopropyl-8-[3,4-di(3-hydroxypropyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-2,2-dimethyl-ethyl)]-amide;

5(S]-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-(3-N-methylcarbamoyl-propyl)-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-2-morpholinoethyl)amide;

5(S)-amino-4(S)-hydroxy-2(S). 7(S)-diisopropyl-8-[4-(2-morpholinoethoxy)-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-2,2-dimethyl-ethyl)]-amide;

[5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[3-(3-methoxypropyloxy)- 4,5-ethylenedioxy-phenyl]-octanoic acid (N-2-morpholinoethyl)amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[3-(3-methoxypropyloxy)- 4,5-ethylenedioxy-phenyl]-octanoic acid [N-(2-carbamoyl-2.2-dimethyl-ethyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[3-(3-methoxy-propyloxy)- 4,5-methylenedioxy-phenyl]-octanoic acid (N-2-morpholinoethyl)amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[3-(3-methoxypropyloxy)- 4,5-methylenedioxy-phenyl]-octanoic acid [N-(2-carbamoyl-2.2-dimethyl-ethyl)]amide;]

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-2,2-ethylene-ethyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-prop oxy)-phenyl]-octanoic acid [N-(3(S)-2-oxo-pyrrolidin-3-yl-methyl)]amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(4-methoxy-but-2-eneoxy)-phenyl]-octanoic acid (N-butyl)amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-hydroxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-H-benzyloxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[3,4-di(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(2,2,2-trifluoroethoxy)- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(3-hydroxy-propyloxy)- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(2-amino-ethoxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(5-amino-pentyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(4-amino-butyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(4-N,N-dimethylamino-butyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-{4-[4-N-(trifluoromethane-sulfonylaminobutyloxy)-3-(3-methoxypropyloxy)-phenyl]}-octanoic acid (N-butyl)-amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-carboxymethoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(3-ethoxycarbonyl-propyloxy)- 3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(3-carboxy-propyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(4-methoxycarbonylbutyloxy)- 3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(4-carboxy-butyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(2-methoxymethoxy-ethyl)-phenyl]-octanoic acid (N-butyl)amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-(3-hydroxypropyloxy)-3-(methoxypropyloxy)-phenyl]-octanoic acid N-(2-morpholinoethyl)amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-[2-(4-hydroxypiperidin-1-yl)ethyl]amide dihydrochloride;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-[2-(trans-2,6-dimethyl-morpholino)ethyl]amide;

5(S)-am in o-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-me propyloxy)-phenyl]-octanoic acid N-[2-(cis-2,6-dimethyl-morpholino)ethyl]amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-(2-piperidinoethyl)amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-[2-(4-methoxypiperidino)-ethyl]-amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-(2-thiomorpholinoethyl)amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(3-hydroxypropyl)]amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(4-acetoxybutyl)]amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(3-cyanopropyl)]amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(3-methoxypropyl)]amide;

5(S)-am no-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-acetylamino-ethyl)]amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid {N-[2-(2-pyridyl)-ethyl]}amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy}-phenyl]-octanoic acid N-[2-(N-oxomorpholino)ethyl]amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid {N-[3-(tert-butylsulfonyl)-propyl]}amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid {N-[3-(ethylsulfonyl)-propyl]}-amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid {N-[2-(ethylsulfonyl)-ethyl]}-amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid {N-[2-(N-butylsulfonyl)-ethyl]}-amide;

[(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid {N-[2-(N,N-dimethylsulfonylamino)-ethyl]}-amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid {N-[3-(1H-tetrazol-5-yl)-propyl]}-amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid {N-[3-(1H-imidazol-5-yl)-propyl]}-amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid {N-[3-(3-methyl-1,2,4-oxadiazol-5-yl)-propyl]}-amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(3-aminopropyl)]-amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-[2-dimethylamino-ethyl)]-amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-(2-morpholinoethyl)amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-(3-morpholinopropyl)amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-[2-(1,1-dioxothiomorpholino)ethyl]amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-(2-ethoxycarbonylethyl)amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-carboxy-ethyl)]-amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(3-methoxycarbonyl-ethyl)]-amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(3-carboxypropyl)]-amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-carbamoylethyl)]-amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(4-carbamoylbutyl)]-amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-{3-[N-(2-methoxyethyl)carbamoyl]propyl}amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-(4-morpholino-4-oxo-butyl)amide;

5(S)-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-2,2-dimethyl-ethyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-(1,1 -dimethyl-2-morpholino-ethyl)amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-[1 (R, S)-methyl-2-morpholino-ethyl]amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(1 -carbamoyl-1 -methyl-ethyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(l-carbamoyl-methyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-ethyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-[2-(N-methyl-carbamoyl)ethyl]amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-(3-morpholino-3-oxo-propyl)amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid {N-[2-(N, N-dimethyl-carbamoyl)-1 (R, S)-methyl-ethyl]}- amide;

(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-1 (R)-isopropyl-ethyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid {N-[2-(N-methylcarbamoyl)-1(R)-isopropyl-ethyl]}-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid {N-[2-(N,N-dimethylcarbamoyl)-I (R)-isopropyl-ethyl]}-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(1(S)-carbamoyl-2-hydroxy-ethyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(, 3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(1(S),2-dicarbamoyl-ethyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(1(S) ,3-dicarbamoyl-propyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(1(S)-carbamoyl-propyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(1(S)-carbamoyl-2(S)-methyl-butyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-[2(R, S)-carbamoyl-2(R, S)-methyl-ethyl]-amide;

5(S)-amino4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-1(S)-methyl-ethyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-1 (R)-methyl-ethyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-[2(S)-carbamoyl-2(S)-methylethyl]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid {N-[2(S)-(N-methyl-carbamoyl)-2(S)-methyl-ethyl]}-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-carboxy-2,2-dimethyl-ethyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-carboxy-2,2-diethyl-ethyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-[(1-carboxy-cyclopentyl)-methyl]amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid {N-[2-(1 H-tetrazol-5-yl)-ethyl]}-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-[1(S)-(5-oxopyrrolidin-2-yl)methyl]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-[1 (R)-(5-oxopyrrolidin-2-yl)methyl]-amide;

5(S)-amine-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-[N-(morpholin-4-yl)carbamoyl-methyl]amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(1(S)-carbamoyl-ethyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-{1(S)-[(N-methyl)-carbamoyl]-ethyl}-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-{1(S)-[(N, N-dimethyl)-carbamoyl]-ethyl}-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-{1(S)-N-[(morpholin-4-yl)-carbamoyl]-ethyl}amide;

5(S)-amino-4(S)-hydroxy-2(S),7 (,S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-[1(S)-carbamoylbutyl]amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-[1(S)-carbamoyl-2-methyl-propyl]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-[1(S)-(N-methylcarbamoyl)-2-methyl-propyl]amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-[1(S)-(N,N-dimethylcarbamoyl)-2-methyl-propyl] amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-{1(S)-[N-(morpholin-4-yl)carbamoyl]-2-methyl-propyl}amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-[2-(N-methylsulfonylamino)ethyl]amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-{2-[N-(morpholin-4-yl)-sulfonyl]ethyl}amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-[(N-acetyl-piperidin-4-yl)methyl]amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(4-methoxy-butyl)-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethylethyl)amide;

5(S),amino,4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-[2-(N,N-dimethylcarbamoyl)ethyl]amide or

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(4-methoxybutyl phenyl]-octanoic acid N-(2-morpholinoethyl)amide,

or in each case a salt thereof,

7. A compound according to claim 1 which is selected from the group consisting of 5(S)-amino-4(S)-hydroxy-2(S), 7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(3(R)-2-oxo-pyrrolidin- 3-yl-methyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(3(S)-2-oxo-piperidin-3-yl-methyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(3(R)-2-oxo-piperidin-3-yl-methyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyl-oxy)-phenyl]-octanoic acid [N-(3-carbamoyl-3,3-dimethyl-propyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(4-methoxy-butyl)phenyl]-octanoic acid [N-(5(S)-2-pyrrolidinon-5-yl-methyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(4-methoxy-butyl)-phenyl]-octanoic acid [N-(5(R)-2-pyrrolidinon-5-yl-methyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(6(S)-2-oxo-piperidin-6-yl-methyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(6(R)-2-oxo-piperidin-6-yl-methyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-thiazol-2-yl-ethyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(4(S)-2-oxazolidinon-4-yl-methyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(4(R)-2-oxazolidinon-4-yl-methyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(3(S)-2.5-dioxo-pyrrolidin-3-yl-methyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(3(R)-2.5-dioxo-pyrrolidin-3-yl-methyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyl oxy)-phenyl]-octanoic acid [N-(2,6-dioxo-piperidin-4-yl-methyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(4(S)-2-oxothiazolidin-4-yl-methyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(4(R)-2-oxothiazolidin-4-yl-methyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(tetrahydro-2-pyrimidon-5-yl-methyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(N-acetyl-2-amino-2-methyl-propyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(N-formyl-2-amino-2-methyl-propyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(4-acetyl-piperazinyl-ethyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2,4-imidazolinedion-5-yl-methyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(4-methoxy-butyl) phenyl]-octanoic acid [N-(2-hydroxy-pyridin-6-yl-methyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2,2-dimethyl-2-sulfamoyl-ethyl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2,2-dimethyl-2-(N,N-dimethyl)-sulfamoyl-ethyl)]-amide hydrochloride;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyl oxy)-phenyl]-octanoic acid [N-(2-oxo-piperidin-3(R)-yl)]-amide;

5(S]-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyl oxy)-phenyl]-octanoic acid [N-(2-oxo-piperidin-3(S)-yl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-oxo-piperidin-4-yl)]-amide;

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(N-acetyl-piperidin-4-yl)]-amide or

5(S)-amino-4(S)-hydroxy-2(S) ,7(S)-diisopropyl-8-[4-methoxy-3-(4-methoxy-but-1 en-yl)-phenyl]-octanoic acid [N-(2-carbamoyl-2,2-dimethyl-ethyl)]-amide

or in each case a salt thereof.

8. A pharmaceutical composition comprising as pharmaceutical active ingredient a compound according to claim **1** in free form or in pharmaceutically acceptable salt form, together with one or more customary pharmaceutical excipient(s).

9. A method of treating hypertension, congestive heart failure, cardiac hypertrophy, cardiac fibrosis, cardiomyopathy postinfarction, nephropathy, vasculopathy, neuropathy, restenosis following angioplasty, raised intra-ocular pressure, glaucoma, abnormal vascular growth, hyperaldosteronism or anxiety states, characterized in that a therapeutically effective amount of a compound according to claim **1** in the free form or in the form of a pharmaceutically acceptable salt is administered to a warm-blooded organism in need of such treatment.

10. A compound according to claim **1** being 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid morpholinopropyl)amide or a salt thereof.

11. A compound according to claim **1** being 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid morpholinoethyl)amide or a salt thereof.

12. A compound according to claim **1** being 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(N-methyl-carbamoyl)- 1 (R, S)-methyl-ethyl]}-amide or a salt thereof.

13. A compound according to claim **1** being 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(3-carbamoylpropyl)amide or a salt thereof.

14. A compound according to claim **1** being 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2(R)-(N-methyl-carbamoyl)- 2(R)-methyl-ethyl]}-amide or a salt thereof.

15. A compound according to claim I being 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-thiomorpholinoethyl)amide or a salt thereof.

16. A compound according to claim I being 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(N, N-dimethyl-carbamoyl)ethyl]amide or a salt thereof.

17. A compound according to claim I being 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoyl-1(R,S)-methyl-ethyl)amide or a salt thereof.

18. A compound according to claim I being 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2(R)-carbamoyl- 2(R)-methyl-ethyl]-amide or a salt thereof.

19. A compound according to claim I being 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethyl-ethyl)amide or a salt thereof.

20. A compound according to claim I being 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(N-acetyl)-piperidin- 4-yl)ethyl]amide or a salt thereof.

21. A compound according to claim **1** being 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[(N,N-dimethyl)-carbamoyl-methyl]}-amide or a salt thereof.

22. A compound according to claim I being 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2(R, S)-(N-methylcarbamoyl)- 2(R,S)-methyl-ethyl]-amide or a salt thereof.

23. A compound according to claim I being 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl- 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethyl-ethyl)-amide or a salt thereof.

24. A compound according to claim **1** being 5(S)-Amino-2(S),7(S)-diisopropyl- 4(S)-hydroxy-8-[4-tert-butyl-3-(3-methoxypropoxy)-phenyl]-octanoic acid [N-2-(morpholin-4-yl)-ethyl]-amide or a salt thereof.

* * * * *

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Alexandria, VA 22313-1450
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APPENDIX E

Customer No 1095 | ISTMT | DATE PRINTED 03/07/2007

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER NJ 07936-1080

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,559,111	**$830.00**	**$0.00**	**03/01/00**	**08/416,242**	**09/24/96**	**04/04/95**	**04**	**NO**	**4-19919/A**

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
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Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,559,111	**$2,090.00**	**$0.00**	**03/02/04**	**08/416,242**	**09/24/96**	**04/04/95**	**08**	**NO**	**4-19919/A**

APPENDIX F

EINGEGANGEN

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 62,976

Speedel Pharma Ltd
Attention: Dimitrios Goundis, Ph.D.
Hirschgaesslein 11
4051 Basel, Switzerland

Dear Dr. Goundis:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 62,976

Sponsor:	Speedel Pharma Ltd
Name of Drug:	Aliskiren hemifumarate (INN); SPP 100B (Code)
Date of Submission:	July 19, 2001
Date of Receipt:	July 23, 2001

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, on or before August 22, 2001 we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will notify you immediately that (1) clinical studies may not be initiated under this IND ("clinical hold") or that (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have notified you that the information you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

IND 62,976

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, to either of the following addresses:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please call me at (301) 594-5334.

Sincerely yours,

Sandra Birdsong
Regulatory Project Manager
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Frank LaSaracina
Speedel Pharmaceuticals Inc.
1661 Route 22 West
Bridgewater, NJ 08807

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sandra Birdsong
7/31/01 10:48:04 AM

APPENDIX G

CHRONOLOGY OF SIGNIFICANT REGULATORY ACTIVITIES BETWEEN APPLICANT AND FDA DURING THE IND AND NDA PERIODS

IND PERIOD

Date	Description of Correspondence
08-Nov-2001	Pre-IND meeting between Speedel Pharma and the Cardio Renal Division.
19-July-2001	Speedel Pharma submits IND to FDA.
23-July-2001	FDA receives IND
10-Aug-2001	Submitted New Protocol 1940-007
04-Sep-2001	Submitted New Protocol SPPCRD11
26-Sep-2001	Submitted New Protocol SPP100CRD15
22-Aug-2002	Submitted Speedel letter to FDA accepting ownership of IND 62,976 for Aliskiren
26-Aug-2002	Letter from Novartis to FDA accepting ownership of IND 62,976 for Aliskiren, a renin inhibitor, from Speedel Pharmaceuticals Inc. of Bridgewater, NJ. On August 22, 2002, Speedel informed the FDA that ownership of the IND has been transferred to Novartis Pharmaceuticals, effective September 1, 2002. Aliskiren will be evaluated in hypertension
05-Sep-2002	FDA LETTER acknowledging receipt of the August 22, 2002 notification of the transfer of sponsorship of Aliskiren (SPP100) from Speedel Pharmaceuticals, Inc., to Novartis Pharmaceuticals. In order to complete its files, the FDA is requesting information as outlined.
17-Sep-2002	Response to FDA letter of September 5, 2002 which acknowledged transfer of the IND from Speedel Pharmaceuticals to Novartis Pharmaceuticals and also requested response to several issues associated with the transfer. The new sponsorship of the IND became effective on September 1, 2002.
30-Oct-2002	FDA LETTER requesting an annual progress report for the IND to include information as outlined.
13-Nov-2002	Annual Report covering the period from August 22, 2001 through August 21, 2002. Included Individual study information, safety , clinical, preclinical information, Investigator's Brochure, edition 6, dated April 2002 and summary of changes from version 5 to version 6.
10-Feb-2003	New Protocol 2201, "A multicenter, randomized, double-blind, placebo-controlled, parallel-group study comparing aliskiren 150 mg, 300 mg and 600 mg to placebo and irbesartan 150 mg in patients with mild to moderate essential hypertension". Investigators: Drs. D.W.Bouda, L.G.Corn, E.Riffer.
19-Feb-2003	Provided documentation to support a revised drug substance synthesis. In addition, documentation to support the composition, manuracturing procedure, specifications and stability for the following is provided: Aliskiren over-encapsulated tablets, 150 mg

	(KN3768785_RD01, 300 mg (KN3768801_RD01, general placebo hard gelatin capsule to match Aliskiren over-encapsulated tablets (KN3755030.029, Irbesartan, comparator (KN3768868_RD01).
10-Mar-2003	New investigators to Protocol 2201: Drs. M.Baron, F.N.Cole, V.M.Figueredo, T.J.Gardner, A.F.Harris, B.Kerzner, M.J.Koren, R.S.Lipetz, F.P.Maggiacomo, A.O.Odugbesan, J.F.Quigley, H.Resnick M.D.Reynolds, J.B.Vogt, J.Wayne, E.Zawada.
19-Mar-2003	New investigators, Protocol 2201: Drs. J. R. Asher, R.Bettis, R.M. Bouvier, R.K. Cady, F.A.Kawley, R.J. Parmer, S.Promisloff, R.F. Stevens, E. Zawada.
11-Apr-2003	Provided carcinogenicity study for special protocol assessment, "104-week oral (feed admixture) carcinogenicity study in rats" and requested agency concurrence with the proposed route of administration and proposed dosage levels". Supportive documents are also included. 3 vols.
15-Apr-2003	New investigators to Protocol 2201: Drs. D.A. Calhoun, L.I. Cowan, A.H. Gradman, J.B. Naidu, R.Z. Paster, S.P. Schmidt, J.Skokan.
09-May-2003	Provided response to FDA request concerning the special protocol assessment submitted on April 11, 2003.
20-May-2003	New investigators, Protocol 2201: Drs. B.E. Chanlder, W.B. White, M.A. Munger.
29-May-2003	FDA FAX responding to the carcinogenicity special protocol assessment request of April 11, 2003.
02-Jun-2003	Response provided to FDA fax of May 29, 2003 which included comments on the special protocol assessment request of April 11, 2003. To concur with FDA request, some adaptations have been made to the carcinogenicity study, however, Novartis does not justify altering the housing of the animals and requests FDA consideration and response.
16-Jun-2003	Correspondence to confirm the resolution reached regarding the issue of housing animals, the subject of the June 2, 2003 correspondence to FDA. As confirmed, Novartis will proceed as planned with paired animals in the study.
17-Jun-2003	New investigators, Protocol 2201: Drs. Jerry R. Mitchell, Hugh C. Palmer.
04-Aug-2003	New investigators for Protocol 2201: Drs. R.M. Zusman, R.J. Womeodu.
14-Oct-2003	Annual Report covering the period from August 22, 2002 through August 21, 2003. Included clinical, preclinical information, revised Investigator's Brochure, dated December 9, 2002.
16-Oct-2003	TELECON WITH FDA to discuss whether a new IND is required for Study 2203 which would assess Aliskiren in the treatment of hypertension and in combination with valsartan as a free-add on agent. The FDA confirmed that the study should be submitted to the existing IND 62,976.
16-Oct-2003	FAX TO FDA to confirm whether Study 2203 to assess combination of Aliskiren and valsartan on blood pressure reduction in patients with essential hypertension, can be submitted to the existing IND 62,976.
19-Dec-2003	Request for a Type B end-of-phase 2 meeting to obtain FDA feedback on the clinical development for aliskiren as an effective and safe antihypertensive.
06-Jan-2004	FDA FAX confirming the meeting scheduled for February 11, 2004 to discuss phase 3 clinical development

	program to support approval.
09-Jan-2004	At the reqeust fo the FDA, provided a summary of completed studies and the Investigator's Brochure.
14-Jan-2004	Provided briefing materials in preparation for the end-of-phase II meeting scheduled for February 11, 2004 to discuss the development plans for Aliskiren
20-Jan-2004	Updated CMC information providing for clinical formulations that will be evaluated in an upcoming clinical trial.
11-Feb-2004	Telecon with the FDA to obtain feedback on the clinical development program to support approval fo aliskiren.
12-Feb-2004	New Protocol 2203 and Amendment 1, "A randomized, double-blind, multicenter, multifactorial, placebo-controlled, parallel-group study to evaluate the efficacy and safety of combinations of aliskiren and valsartan compared with their component monotherapies and the combination of valsartan and HCTZ in hypertensive patients".
05-Mar-2004	FDA FAX which contains the minutes of the meeting with Novartis on February 11, 2004 to discuss the Phase 3 development plan to support approval.
19-Apr-2004	Request for special protocol assessment for Phase II clinical protocol entitled, "An 8 week double-blind, multicenter, randomized, multifactorial, placebo-controlled, parallel-group study to evaluate the efficacy and safety of aliskiren administered alone and in combination with hydrochlorothiazide in patients with essential hypertension".
28-Apr-2004	FDA LETTER indicating that the agency will respond in writing regarding the special protocol assessment request of April 19, 2004, serial no. 027.
06-May-2004	New investigators, Protocol A2203: Drs. A.H.Wong, B.Kerzner, S.B.Jones, L.K.Kamalu, J.Rubino, E.Zawada, J.Mitchell, S.G.Chrysant, M.Baron, R.K.Cady, J.E.Liljenquist, F.P.Maggiacomo, A.Harris.
11-May-2004	New Protocol 2211, "An open label, multiple dose study to evaluate the pharmacokinetic drug-drug interaction between furosemide and aliskiren when given alone or in combination to healthy volunteers". Investigator: Stephen A. Bart.
11-May-2004	Investigator's Brochure, Edition 2, replacing edition 1, release date April 15, 2004.
13-May-2004	Requested FDA concurrence of Novartis' interpretation of FDA's statement in the March 5, 2004 meeting minutes regarding pharmacokinetic interaction with food.
18-May-2004	Request for special protocol assessment for Phase 1 protocol entitled, "A randomized, double blind, multiple oral dose study to evaluate the effects of SPP100 on cardiac subjects vs placebo with positive control (Avelox)".
18-May-2004	New Protocol 2302, "A 12 month, randomized, open-label, multicenter, study to assess the long term safety of aliskiren 150 mg alone and 300 mg alone or with the optional addition of hydrochlorothiazide (12.5 mg or 25 mg) in patients with essential hypertension".
20-May-2004	TELECON WITH FDA discussing development plans for aliskiren and specifically Studies 2204, 2208 and fixed dose combination INDs.
26-May-2004	TELECON WITH FDA inquiring whether further characterization of food effect on aliskiren is required.
26-May-2004	New investigators: Protocol 2203-D.W.Bouda, M.A.Munger, J.E.Pappas, M.J.Koren, A.H.Gradman, M.C.Portz, J.L.Pool, M.Guice, D.A.Calhoun, R.M.Karns, W.R.Detten,

	R.F.Stevens, G.H.Fischer, H.J.Downey.
26-May-2004	New Protocol 229, Parts A and B, "An open label, parallel-group study to compare the pharmacokinetics and pharmacodynamics of a single dose of SPP 100 (Aliskiren) between healthy subjects and type 2 diabetic patients". Investigator: Lawrence A. Galitz,.
27-May-2004	In reference to CMC issues that require discussion with FDA, Novartis is providing the agency a top line summary of the information which will be contained in the upcoming CMC Briefing Book to determine whether a teleconference is needed to discuss the issues.
27-May-2004	FDA LETTER concluding that the May 18, 2004 request for special protocol assessment , Serial no. 033, does not qualify for special protocol assessment.
27-May-2004	Updated preclinical safety information , Study Nos. 0250463 and 0413049.
03-Jun-2004	FDA LETTER providing response to questions included in the special protocol assessment request dated April 19, 2004, serial No. 027.
07-Jun-2004	Documentation to support the following formulations: SPP100 film coated tablets, 75 mg, KN 3764313.004; 150 mg KN, 3765070.005; 300 mg, KN 6000937.004; Hydrochlorothiazide 12.5 mg capsule, KN 3753696.002; 25 mg capsule, KN 3753688.002.
09-Jun-2004	TELECON WITH FDA regarding the CMC general correspondence submitted on May 27, 2004 and submission of a meeting request to discuss CMC issues.
16-Jun-2004	Administrative memo clarifying two statements regarding Study 2204 submitted on April 19, 2004, serial no. 027.
17-Jun-2004	FDA LETTER responding to the questions included in the May 18, 2004 submission, serial no. 033, which included a special protocol assessment request.
18-Jun-2004	Request for clarification on several points in FDA's response to the special protocol assessment request dated June 3, 2004. Also included Novartis' plan to address FDA's recommendations.
21-Jun-2004	Request a Type A meeting to discuss the Division's response to the special protocol assessment request received June 3, 2004.
22-Jun-2004	New investigators-Protocol 2203: M.J.Budoff, W.B.White. Protocol 2302: H.R.Knapp, A.H.Wong, M.C.Portz, R.G.DeGarmo, J.R.Herron, K.M.Sheehan, S.G.Swanson, J.E.Greenwald, C.Nelson, A.Areephanthu, E.B.Portnoy, K.Sall, J.F.Quigley, C.P.Griffin, G.A.Tarshis, J.Mazza, M.S.Oberoi, B.Kerzner, J.R.Mitchell, M.E.Shirley, A.Barreto, A.J.Mollen, A.J.Slaski.
22-Jun-2004	TELECON WITH FDA regarding a teleconference to clarify the written response on June 21, 2004, Study 2204 and amendment to Aliskiren DDI Study 2211 with furosemide.
25-Jun-2004	FDA FAX confirming the July 12, 2004 teleconference in response to the June 24, request to discuss the Division's special protocol assessment responses.
29-Jun-2004	Administrative memo describing typographical errors which occurred in the May 11, 2004 submission which included Study 2211, serial no. 030.
30-Jun-2004	Briefing book submitted in preparation for the meeting scheduled for July 12, 2004 to discuss the special protocol assessment comments to Study 2204.
16-Jul-2004	New investigators, Protocol 2302: M.U.Weerasinghe, M.E.Hamilton, R.S.Lipetz, R.J.Emery, S.C.Sharp, J.Pullman, S.A.Bart, D.L.Fried, L.C.Bass, M.J.Noss, L.F.Feld, C.H.Booras, T.L.Poling, H.F.Farmer, J.G.Pottanat, W.L.Gray, J.T.Forsythe, M.Baron.

20-Jul-2004	Protocol 2302, Amendment No. 1.
21-Jul-2004	Advance notification to the Division of a carcinogenicity protocol submission in September 2004 with a request for a special protocol assessment.
21-Jul-2004	Request agency acknowledgment in writing of the deferral of pediatric assessments requested verbally during the end of phase 2 meeting.
28-Jul-2004	FDA FAX providing the minutes of the teleconference held on July 12, 2004 to clarify the Division's reponses to the Special Protocol Assessment.
29-Jul-2004	Novartis' minutes of the Special Protocol Assessment teleconference with FDA on July 12, 2004.
05-Aug-2004	Changes in FDA Form 1572 for Protocol 2203.
09-Aug-2004	New investigators, Protocol 2204: L.I.Gilderman, R.D.Madder, L.Anastasi, S.G.Chrysant, T.D.Klein, S.Babazadeh, D.E.Mansfield, H.Resnick, M.B.Samson. Protocol 2302: A.H.Gradman, J.P.Gresh, P.W.Wallace, M.J.Lillestol, K.Vijayaraghavan.
09-Aug-2004	Protocol 2204, Post-text supplement 1.
17-Aug-2004	Provided additional CMC information requested by the Agency at the February 11, 2004 End-of-Phase 2 meeting. Additionally, Novartis is requesting a teleconference with the FDA to discuss CMC issues.
19-Aug-2004	New investigators, Protocol 2204: G.T.Connor, J.N.Tarro, K.Sall, D.B.Witkin, R.M.Bouvier, B.C.Pogue, A.L.Phillips, D.A.Calhoun, M.R.Seidner, D.P.Zmolek. Protocol 2302: G.E.Godoy, O.Shemisa, M.Kaye.
26-Aug-2004	FDA LETTER agreeing that a deferral of pediatric studies in patients < 1 month to 16 years of age is justified in reference to the July 21, 2004 request.
31-Aug-2004	Documentation providing CMC information on clinical formulations to be used in an upcoming clinical trial.
01-Sep-2004	FDA FAX confirming the meeting scheduled for September 22, 2004 to discuss CMC requirements for filing the NDA.
13-Sep-2004	New Protocol 2201, "A multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the effects of aliskiren on proteinuria when added to standardized losartan therapy and optimal antihypertensive therapy in patients with hypertension and Type 2 diabetes mellitus". Protocol 2307, Post-Text supplement 1, Pharmacogenetics sub-study.
21-Sep-2004	New Protocol 2228, "An open label, multiple dose study to evaluate the pharmacokinetic drug-drug interaction between hydrochlorothiazide and aliskiren when given alone or in combination to healthy volunteers".
21-Sep-2004	New investigators-Protocol C2201: R..K.Cady, D.G.Robertson, E.D.Himot, S.P.Schmidt, W.A.Spisak, J.E.Mossberg, R.J.Graf, M.R.Seidner, K.R.Cohen, K.Hillner, R.A. Sachson, R.S.Lipetz, K.Carpenter. Protocol 2204: A.Forker, D.H.Sugimoto, J.E.Gutmann, A.V.Rao, R.B.Christensen, W.Drummond, J.R.LaSalle, R.Fuchs, R.E.Mills. Protocol 2302: A.R.Zanabli, J.L.Pool, D.Sica.
22-Sep-2004	Request for special carcinogenicity protocol assessment for Studies: 1940/14, 1940/49, 0201416; 1940/19, 0470069. Additionally included Investigator's Brochure, Dose justification study and questions for the Agency.
24-Sep-2004	New Protocol 2308, "An eight-week, randomized, double-blind, placebo-controlled, parallel-group multicenter study comparing aliskiren 150 mg, 300 mg and 600 mg to placebo in patients with essential hypertension".
24-Sep-2004	New Protocol 2208, "A randomized, double-blind, multiple oral dose study to evaluate the effects of

	SPP100 on cardiac safety in healthy subjects vs placebo with positive control (Avelox)".
28-Sep-2004	FDA's minutes of the September 22, 2004 meeting requested by Novartis to obtain Agency feedback on specific CMC issues as recommended in the End of Phase 2 meeting on February 11, 2004.
29-Sep-2004	Addendum to special carcinogenicity protocol assessment submitted on September 22, 2004, serial no. 059, which contains the complete report for Study No. 0470069 entitled, "4-week oral (diet) range-finding toxicity study in CB6F1 wild-type mice".
29-Sep-2004	FDA LETTER indicating that the September 22, 2004 request for special carcinogenicity protocol assessment, serial no. 059, is under review and a response will be provided in writing within 45 days of its receipt.
30-Sep-2004	Documentation providing CMC information on clinical formulations that will be used in an upcoming clinical trial.
01-Oct-2004	TELECON WITH FDA discussing the carcinogenicity protocol special protocol assessment request dated September 22, 2004.
11-Oct-2004	Amendment to Protocol 2228 to add Part B; administrative and GCP instruction and amendment to Protocol 2308 to add an administrative memo. Also informed the FDA that Protocol 2201, submitted September 13, 2004, should be referred to as C2201.
12-Oct-2004	As requested by the pharmacology reviewer of the carcinogenicity protocol submitted on September 22, 2004, provided the first interpretable results of the study.
14-Oct-2004	Novartis' minutes of the Type B CMC teleconference to gain FDA agreement on CMC issues.
15-Oct-2004	New investigators, Protocol C2201: J.E.Liljenquist, A.Barreto, M.C.Hagan, J.R.LaSalle. Protocol 2208: R.M.Fleischmann, M.Sack, H.F.Farmer. Protocol 2228: D.D.Hoelscher. Protocol 2308: J.R.Herron, D.M.Brandon, M.H.Link, T.Hart, F.S.Eder.
15-Oct-2004	Dr. Frank Farmer. Cerebrovascular accident, cerebral infarction, hemiparesis, paraesthesia.
19-Oct-2004	Annual Report covering the period from August 22, 2003 through August 21, 2004. Included clinical information, revised Investigator's Brochure, preclinical information.
29-Oct-2004	FDA FAX which includes executive CAC recommendations and conclusions in response to the carcinogenicity special protocol assessment request.
05-Nov-2004	In response to FDA concerns received verbally concerning the design of Study 2208, serial no. 033, Novartis presented its rationale for its choice of a parallel design for the study and commented on FDA's parmacokinetic/pharmacodynamic recommendations.
08-Nov-2004	New Protocol 2214 and Amendment no. 1, "An open label, multiple dose study to evaluate the pharmacokinetic drug-drug interaction between Lanoxin (digoxin) and aliskiren when given alone or in combination to healthy volunteers".
16-Nov-2004	New Protocol 2220, "An open label, multiple dose study to evaluate the pharmacokinetic drug-drug interaction between metformin and aliskiren when given alone or in combination to healthy volunteers".
17-Nov-2004	TELECON WITH FDA discussing the design of QT Study 2208 on October 28 and November 16 and 17, 2004.
17-Nov-2004	New Protocol 2221, "An open-label, multiple-dose study

	in normal healthy volunteers to evaluate the pharmacokinetics, safety and tolerability of SPP 100 (Aliskiren) and ramipril (Atlace) administered alone and in combination".
22-Nov-2004	New investigators, Protocol C2201: A.G.Wynne, J.T.Lane, R.Cooper, R.Busch, C.S.Ghosh, J.Robertson. Protocol 2204: R.M.Vicari, M.R.Wofford, D.E.Wise. Protocol 2214: M.D.Reynolds. Protocol 2307: L.E. Mansfield, J.Dexter, J.R.LaSalle, C.Superczynski, B.Kerzner, H.D.Storch, E.A.Marks. Protocol 2308: D.Sugimoto, J.E.Pappas, M.L.Look, P.Rosenblit, W.L.Gray, A.Puopolo, D.E.Loew, K.D.Klatt, J.M.Neutel, L.R.Popeil, S.A.Wilson, J.E.Fanning, D.G.Wolinsky, C.Buettner, B.A.Wittmer, R.Blasini, R.Busch, T.Marbury, J.Mitc
23-Nov-2004	In response to FDA verbal communication advising Novartis that Protocol 2208, for which the FDA raised concerns regarding the design, should proceed with the current design, Novartis considers the matter closed and Study 2208 will continue unchanged.
08-Dec-2004	New investigators, Protocol 2201: M.S.Rendell, B.C.Wood, N.Kopyt. Protocol 2220: M.D.Reynolds. Protocl 2221: J.Ruckle. Protocol 2307: R.D.Ward, E.J.Busick. Protocol 2308: P.D.Toth, M.A.Zinny, K.S.Self, R.Caso, P.Narayan, R.H.Farsad.
15-Dec-2004	Updated CMC information providing information on clinical formulations that will be evaluated in clinical trials.
17-Dec-2004	New protocols, 2304, "A twelve-week, randomized, double-blind, parallel-group, multicenter, dose escalation study to evaluate the efficacy and safety of aliskiren administered alone and in combination with atenolol in patients with essential hypertension". Protocol 2305, "A six-week, randomized, double-blind, parallel-group, multicenter study to evaluate the safety and efficacy of the combination of aliskiren 150 mg and amlodipine 5 mg compared to amlodipine 5 mg and 10 mg in hypertensive patients not adeq
22-Dec-2004	TELECON WITH FDA regarding the design of drug-drug interaction Study 2221 (aliskiren and ramipril) submitted November 17, 2004.
23-Dec-2004	[Peru] Dr. Augusto Chois. Cerebrovascular accident, disease progression, proctalgia, headache, asthenia, hemiparesis, cerebral infarction.
29-Dec-2004	[Peru] Dr. Augusto Chois. Cerebrovascular accident, disease progression, proctalgia, headache, asthenia, hemiparesis, cerebral infarction. Follow up # 1.
07-Jan-2005	New investigators, Protocol C2201: R.Solomon, J.Calles-Escondon. Protocol 2204: J.L.Pool. Protocol 2307: J.R.Mitchell, W.R.Detten, A.Green. Protocol 2308: M.S.Weinberg, J.L.Hargrove.
12-Jan-2005	New Protocol 2216, "An open label, multiple dose study to evaluate the pharmacokinetic drug-drug interaction between valsartan and aliskiren when given alone or in combination in healthy volunteers".
24-Jan-2005	Request Type B meeting to obtain Agency feedback on the development program to support approval of the aliskiren/valsartan fixed combination product.
31-Jan-2005	FDA FAX confirming the pre-IND type B meeting scheduled for March 30, 2005 to discuss the development plan for Aliskiren/valsartan fixed dose combination tablets.
31-Jan-2005	New investigators, Protocol C2201: R.M.Culpepper, J.A.Robinson. Protocol 2216: S.L.Schwartz. Protocol 2305: R.D.Madder, J.K.Heacock, J.R.Herron, W.Drummond, C.Brown, B.Wieskopf, P.C.Ogden, D.F.Phillips,

	J.A.Hoekstra, M.Edris, M.J.Tonkon, J.West. Protocol 2307: C.Kilo. Protocol 2308: R.M.Culpepper.
01-Feb-2005	New Protocol 2306, "A 26 week, double-blind, randomized, multicenter, parallel group, active-controlled study comparing aliskiren to ramipril with optional addition of hydrochlorothiazide, followed by a 4 week double-blind, randomized, placebo-controlled withdrawal in patients with essential hypertension".
04-Feb-2005	Amendment 1 to Protocols 2305 and 2308.
09-Feb-2005	[Peru] Dr. Augusto Chois, Cerebrovascular accident, disease progression, proctalgia, headache, asthenia, hemiparesis, cerebral infarction. Follow-up # 2.
14-Feb-2005	[Peru] Dr. A.Chois. Cerebrovascular accident, disease progression, proctalgia, headache, asthenia, hemiparesis, cerebral infarction.
17-Feb-2005	Dr. Frank Farmer. Cerebrovascular accident, disease progression, cerebral infarction, hemiparesis, paraesthesia. Follow-up # 1.
21-Feb-2005	New Protocol 2218, "An open label, multiple dose study to evaluate the pharmacokinetic drug-drug interaction between amlodipine and aliskiren when given alone or in combination to healthy volunteers".
24-Feb-2005	New investigators: Protocol 2303-R.M.Smith. Protocol 2305: H-U Rashid, J.R.Mitchell, J.Gaffney, S.Sharma, N.K.Shemonsky, M.Nallasivan, R.A.Levy, J.F.Quigley, C.Knight. D.F.Phillips. Protocol 2306: L.I.Cowan, A.H.Wong, S.Kahney, B.M.Zamora, D.A.Kushner, M.A. Canossa-Terris, E.B.Protnoy, J.R.Allison, C.H.Grossman, V.F.Petraglia, E.M.Dyess. Protocol 2307: A.A.Taylor.
28-Feb-2005	Documentation to support drug substance and drug product formulations: Aliskiren drug substance 3000940, synthesis B, Amlodipine 5 mg and 10 mg over encapsulated tablet, KN 3763141.006 and KN 3766896.003 respectively.
02-Mar-2005	[Peru] Dr. S. Campodonico. Myelitis transverse, monoparesis, constipation, back pain, urinary retention, demyelination.
02-Mar-2005	New Protocol 2210, "An open-label, single-dose, parallel-group study to assess the pharmacokinetics of SPP100A in subjects with impaired hepatic function in comparison with healthy controls".
07-Mar-2005	Letter confirming the meeting with the Division scheduled on March 30, 2005 to obtain feedback on the preclinical, clinical, and biopharmaceutical development program for aliskiren fixed combination. A briefing book is included.
09-Mar-2005	[Peru] Dr. S.Campodonico. Myellitis transverse, monoparesis, constipation, back pain, urinary retention, demyelination. Follow-up # 1.
16-Mar-2005	[Peru] Dr. A. Chois. Cerebrovascular accident, disease progression, proctalgia, headache, asthenia, hemiparesis, cerebral infarction. Follow-up # 4.
18-Mar-2005	Adminstrative memos describing additional clarifications in Protocol 2307.
18-Mar-2005	Correspondence addressing issues relating to the aliskiren NDA that Novartis plans to submit first quarter of 2006.
18-Mar-2005	New Protocol 2217, Parts A and B, "An open-label single dose study assessing the effect of age on the pharmacokinetics of SPP100".
21-Mar-2005	[Peru] Dr. S. Campodonico. Myelitis transverse, monoparesis, constipation, back pain, urinary retention, demyelination. Follow-up # 2.
25-Mar-2005	New investigators, Protocol C2201: P.A.Crawford,

	J.Mageli. Protocol 2218: L.A.Galitz. Protocol 2305: J.N.Diamond, E.T.Zawada, S.E.Conrad, M.F.Wilson. Protocol 2306: D.R.Schumacher, L.I.Gilderman, M.Ashraf, G.K.Hilliard, B.D.Snyder, M.F.Wilson, A.H.Gradman, J.G.Thorne, G.Pineless, J.R.Herron, J.R.Cook, A.M.Sussman, D.Linden, J.Champlin, A.A.Carr, R.Jordan, C.Naden, E.P.Boling, W.H.George, A.V. Rao, A.F.Harris, A.D.Puopolo, P.Breaux, J.Mitchell, R.W.Drueding, B.Kerzner, P.J.Troia. Protocol 2308: G.L.Bakris,
28-Mar-2005	FDA FAX confirming the teleconference scheduled for April 20, 2005 to discuss the aliskiren NDA Novartis is planning to submit.
04-Apr-2005	Briefing materials for the teleconference to be held on April 20, 2005 to discus the aliskiren pre-NDA.
07-Apr-2005	Correspondence updating the Division on a CMC issue discussed at the September 22, 2004 teleconference regarding the mutagenic potential of the synthesis intermediate of aliskiren.
08-Apr-2005	New Protocol 2207, Parts A and B, "A randomized, open-label, single-dose, two-period, crossover study in healthy subjects to evaluate the effect of food on the SPP100 Final Market Image (FMI) tablet".
11-Apr-2005	New Protocol 2310, "A 12-week, randomized, double-blind, placebo controlled, parallel group study evaluating the efficacy and safety of aliskiren in patients with diabetes and hypertension of adequately responsive to the combination of valsartan 160 mg and hydrochlorothiazide 25 mg".
12-Apr-2005	New Protocol 2309, "A 12-week randomized double-blind parallel group study to evaluate the efficacy and safety of the combination of aliskiren with HCTZ compared to irbesartan or amlodipine with HCTZ or HCTZ alone in hypertensive patients with BMI>=30 kg/m2 not adequately responsive to HCTZ 25 mg".
19-Apr-2005	FDA FAX which includes minutes of the pre-NDA meeting with the sponsor held on March 30, 2005 to discuss the development plan for fixed-dose combination of aliskiren/valsartan and aliskiren/hydrochlorothiazide.
20-Apr-2005	FDA FAX providing additioal information that the Office of Drug Safety asked to be included in the minutes of the March 30, 2005 meeting.
21-Apr-2005	Toxicology report entitled, "Expert statement and toxicological assessment of SPPI100-B7 (A4), Aliskiren drug substance intermediate".
21-Apr-2005	Protocol 2201, Amendment 1.
22-Apr-2005	New investigators, Protocol 2201: C.V.Ram. Protocol 2210: D.Carter. Protocol 2305: M.A.Munger. Protocol 2306: D.W.Cardona, S.J.Eisenberg, R.E.Swint.
22-Apr-2005	[Brazil] Dr. F.A.Almeida. Affective disorder, psychotic disorder, delirium, mental disorder, feelling abnormal, crying, movement disorder, dysarthria.
25-Apr-2005	[Peru] Dr. S.Campodonico. Multiple sclerosis, myelitis transverse, monoparesis, constipation, back pain, urinary retention, demyelination, paraparesis, hyperreflexia, extensor plantar response. Follow-up #3.
26-Apr-2005	FDA FAX which includes the minutes of the pre-NDA meeting on April 20, 2005 discussing NDA formatting issues for aliskiren and gain Division concurrence with Novartis' proposed strategy for pooling efficacy and safety data.
02-May-2005	New investigators, Protocol 2201: R.Ouseph, B.M.Zamora. Protocol 2207: S.L.Schwartz. Protocol 2217: M.A.Saltzman. Protocol 2306: B.M.Egan, M.D.Lurie, D.A.Calhoun, T.D.Giles. Protocol 2310: C.M.Farrington,

	W.P.Gilbert, T.C.Fagan, R.H.Greengold, R.E.Mills, M.B.Samson, J.H.Mersey, R.Cheriyan, S.E.Conrad, W.Drummond, J.M.Neutel, D.J.Morin, V.Brandenburg.
02-May-2005	Protocol 2302, Amendment 2.
09-May-2005	Updated Investigator's Brochure, Edition 4, release date April 14, 2005.
11-May-2005	New Protocol 2327, "An 8-week randomized, double-blind, parallel group, multicenter, placebo and active controlled dose escalation study to evaluate the efficacy and safety of aliskiren (150 mg and 300 mg) administered alone and in combination with valsartan (160 mg and 320 mg) in patients with hypertension". Investigators: S.Lee-Rugh, J.T.Farrell, F.A.Kawley.
11-May-2005	Correspondence requesting clarification on two points in the minutes of the pre-NDA teleconference on April 19, 2005. Specific reference is made to the submission of raw PK data for all studies and a situation concerning a study that could be submitted at the time of the 120 Day Safety Update.
19-May-2005	[Netherlands] D.Lansdorp. Depression suicidal.
23-May-2005	[Brazil] Dr. F.Almeida. Cerebrovascular accident, affective disorder, psychotic disorder, delirium, mental disorder, feeling abnormal, crying, movement disorder, dysarthria, memory impairment. Follow-up # 1.
24-May-2005	New Protocol 2234, An open-label, multiple-dose study in healthy volunteers to evaluate the pharmacokinetics, safety and tolerability of SPP100 (Aliskiren) and Lipitor (Atorvastatin) administered alone and in combination.
25-May-2005	Correspondence providing an administrative records of a telephone conversation on May 24, 2005, regarding submission of raw PK data conducted by Speedel, the original IND holder, and a study assessing the additivity of aliskiren in combination with Diovan submitted at the time of the safety update, letter dated May 11, 2005.
25-May-2005	[Sweden] Dr. F.Huss. nerve paresis, dizziness, diplopia.
26-May-2005	Dr. F. Farmer. Cerebrovascular accident, disease progression, cerebral infarction, hemiparesis, paraesthesia. Follow-up # 2.
02-Jun-2005	[Sweden] Dr. F.Huss. IIIrd nerve paresis, dizziness, diplopia. Follow-up # 1.
03-Jun-2005	[Netherlands] D.Lansdrop. Depression suicidal. Follow-up # 1.
03-Jun-2005	Amendment which contains documentation to support drug product formulations. There has been a minor change in the manufacturing process of the SPP100 tablets and drug product specifications have been updated and additional stability data is provided.
07-Jun-2005	New investigators, Protocol 2302: D.H.Prichard. Protocol 2305: D.Sugimoto. Protocol 2306: G.L.Barkis, J.R.Allison, C.Naden. Protocol 2310: F.Kozlowski, R.D.Smith, R.J.Emery, F.P.Johnson. Protocol 2327: S.Babazadeh, S.Lewis, R.D.Nielsen, P.C.Ogden, S.Yarows, J.L.Miller, C.Woodruff, J.R.Beymer, T.M.Koehler, T.L.Poling, K.R.Rigonan, J.D.Wayne, R.West, D.Young, M.F.Carter, D.Dobratz, C.Fisher, R.A.Craven, B.Sakran, C.Kilo, S.T.Verzosa, A.Patel, J.K.Sia, T.G.Shetter, N.Lunde, D.C.Subich, J.Mageli, A.Mercado, J.
14-Jun-2005	Draft amendment proposing to revise the sample size estimate for Study 2208 based on the new preliminary FDA guidance
20-Jun-2005	FDA LETTER commenting on the April 21, 2005 submission

	containing a toxicology report, serial no. 108.
27-Jun-2005	New investigators, Protocol 2201: A.C.Thieneman. Protocol 2234: A.L.Laurent. Protocol 2305: A.M.Adelizzi. Protocol 2306: M.H.Weinberger, K.C.Ferdinand, J.Mitchell. Protocol 2310: J.S.Austin. Protocol 2327: J.K.Dexter, J.Schmidt, M.A.Cromer, D.G.Cheung, R.M.Karns, S.Kobylinski, M.C.Portz, C.Ellis, J.W.Sensenbrenner.
27-Jun-2005	FDA LETTER providing comments and recommendations pertaining to the May 2, 2005 amendment, serial no. 112, containing a protocol amendment for Study 2302.
28-Jun-2005	[Netherlands] D.Lansdorp. Depression suicidal, blood glucose abnormal, cholelithiasis, hepatic function abnormal. Follow-up # 2
07-Jul-2005	[Netherlands] D.Lansdorp. Depression suicidal, blood glucose abnormal, cholelithiasis, hepatic function abnormal. Follow-up 3.
12-Jul-2005	Request for a Type A meeting to resolve a recent issue concerning the blinding of clinical supplies in the sponsor's Phase 3 program and FDA recommendation for a bioequivalence study to resolve the issue.
12-Jul-2005	New investigators, Protocol 2201: R.Cherlin, P.A.Snell. Protocol 2210: T.C.Marbury. Protocol 2217: J.Ruckle. Protocol 2305: M.L.Look, P.T.Stearns, R.J.Lockwood, K.Pierce, J.D.Williams. Protocol 2310: L.I.Gilderman, A.Graff. Protocol 2327: C.W.Stanford, T.Rossiter, M.S.Weinberg, M.Jabro, J.Detwiler, J.Cheirif, C.S.Ghosh, D.B.Kaner, R.Fuchs, J.S.Godfrey, H.J.Fields.
15-Jul-2005	[Netherlands] D.Lansdorp. Depression suicidal, disease progression, blood glucose abnormal, cholelithiasis, hepatic function abnormal. Follow-up # 4.
15-Jul-2005	Letter acknowledging agreements reached between Novartis and the Division for ongoing clinical study 2208 submitted on September 24, 2004, serial no. 061 and amended on June 14, 2005, serial no. 127. Novartis was advised verbally that review of the amendment was complete and based on this outcome, the trial will proceed with the amended design.
26-Jul-2005	FDA FAX confirming the meeting rescheduled for August 29, 2005 to resolve issues related to establishing bioequivalence between the formulations used in the clinical trials and to be marketed formulations.
28-Jul-2005	Letter to obtain clarification regarding recommendations in FDA's June 27, 2005 letter regarding rebound effects from aliskiren withdrawal.
04-Aug-2005	[France] Dr. A.Lion. Oedema peripheral, dyspnoea exertional, weight increased.
11-Aug-2005	New investigators, Protocol C2201: A.M.Heller, M.L.Henderson, E.M.Dyess, N.Sapin, M.L.Reeves, P.Suchinda. Protocol 2217: P.A.Chandler. Protocol 2302: J.B.Eberly. Protocol 2305: S.Blumentahl, J.Rubino. Protocol 2310: B.C.Pogue. Protocol 2327: W.M.Miller, S.Oparil, P.August, R.D.Smith, J.R.Mitchell, D.Bernstein, A.M.Porter, M.A.Barber, M.W.Warren, C.A.Mayorga, A.McCain.
12-Aug-2005	Briefing materials for the meeting scheduled to take place on August 29, 2005 to resolve an emergent issue regarding the blinding of clinical supplies in the aliskiren Phase 3 program.
18-Aug-2005	[France] Dr. A. Lion. Angioneurotic oedema, oedema peripheral, weight increased, dyspnoea exertional. Follow-up # 1.
26-Aug-2005	[South Africa] Dr. D.Lakha. Angioneurotic oedema, dyspnoea, throat tightness, anxiety, oropharyngeal

	swelling.
02-Sep-2005	New Protocol to Study No.CSPP100A2334 (Part A) entitled, "An open-label, multiple-dose study to evaluate the pharmacokinetics, safety and tolerability of SPP100 (Aliskiren) when given alone and in combination with Ketoconazole to healthy volunteers.
06-Sep-2005	FDA FAX containing the minutes of the August 29, 2005 Type A meeting with the sponsor discussing the request for a waiver from the conduct of a bioequivalence study to compare the non-encapsulated tablet to the over-encapsulated tablet used for blinding in the clinical studies.
08-Sep-2005	New investigators, Protocol C2201: R.D.Toto. Protocol 2327: B.Samuels, S.A.Atlas, M.Nielsen. Additionally, provided for changes in FDA Form 1572 for Protocols 2302, 2305 and 2306.
08-Sep-2005	Bioequivalence protocol, study 2343, submitted for FDA review in follow-up to the August 29, 2005 meeting during which the Division determined that a bioequivalence trial comparing the non-encapsulated and over-encapsulated tablets of aliskiren is appropriate.
08-Sep-2005	[France] Dr. A.Lion. Scleroedema, anorexia, inflammation, hypertrichosis, tachycardia, skin lesion, oedema peripheral, eyelid oedema, weight increased, dyspnoea exertional, weight decreased, macrocytosis, C-reactive protein increased. Follow-up # 2.
09-Sep-2005	New Protocol 2328 and Amendment 1, "A randomized, double-blind, placebo-controlled, parallel-group, multicenter study comparing an eight-week treatment of Aliskiren 75 mg, 150 mg and 300 mg to placebo in patients with essential hypertension".
12-Sep-2005	[Denmark] Dr. T.Sandager. Angioneurotic oedema, face oedema, stridor.
13-Sep-2005	Administrative Amendment 1 for Protocol 2334.
15-Sep-2005	New Protocol 2331, " An eight week, randomized, double-blind, parallel-group, multicenter study to evaluate the efficacy and safety of the combination of aliskiren/valsartan/HCTZ (300/320/25 mg) compared to the combinations of aliskiren/HCTZ (300/25 mg) and valsartan/HCTZ (320/25 mg) in patients with essential hypertension not adequately responsive to HCTZ 25 mg". Post-text supplement 1: Optional exploratory biomarker study for CSPP100A2331.
15-Sep-2005	Letter acknowledging agreements reached between Novartis and the Division regarding the assessment of possible rebound effect in the aliskiren clinical program in reference to the initial correspondence , serial no. 135.
19-Sep-2005	Protocol 2208, Amendment no. 2.
19-Sep-2005	[DENMARK] Dr. Torben Sandager: Angioneurotic oedema, face oedema, stridor; Follow-up#1.
20-Sep-2005	New Protocol 2343, "An open-label, randomized, single-dose, crossover, replicate study to demonstrate the bioequivalence between the final market image (FMI) tablet of aliskiren and overencapsulated tablets of aliskiren". Parts A and B.
20-Sep-2005	Correspondence to request clarification regarding the conclusions/recommendations section of the Division's August 29, 2005 meeting minutes and to provide additional information for the administrative record.
21-Sep-2005	Protocol 2334, Amendment no.2.
22-Sep-2005	Protocol 2343, Amendment no. 1.
30-Sep-2005	New investigators, Protocol C2201: R.Butin. Protocol 2310: J.M.Flack, B.Kamdar. 2327: L.M.Prisant,

	T.A.Barringer. 2328: H.F.Farmer, W.L.Gray, E.F.Berberabe, L.G.Lapuz, S.D.Folkerth, J.Christensen, R.Cain, A.Graff, L.I.Gilderman, A.L.Free, D.C.Pan, W.R.Cook, M.S.Wukelic, P.T.Stearns, A.J.Slaski, G.E.Poss, B.G.Rankin, S.Ong, S.C.Bowman, G.T.Serfer, A.Reymunde, D.A.Williamson, K.B.Rock. 2331: J.Azocar, S.G.Swanson, T.R.Smith, A.M.Roselli, M.B.Samson, J.B.V.Tanus, P.C.Ogden, J.E.Sutherland, S.C.Sharp, G.A.Tars
03-Oct-2005	New Protocol 2318, "A single center, placebo-controlled study of the effects of ascending single oral doses of Aliskiren compared with Captopril on renal hemodynamics in healthy volunteers on a low and high sodium diet".
04-Oct-2005	Information amendment, Toxicology report 0412013, Mutagenicity test using Salmonella typhimurium.
04-Oct-2005	[DENMARK] Dr. Torben Sandager: Angioneurotic oedema, face oedema, stridor; Follow-up#2.
05-Oct-2005	Annual Report covering the period from August 22, 2004 through August 21, 2005. Also included administrative memo addressing inconsistencies identified in the report. Included clinical, preclinical, CMC information and revised Investigator's Brochure dated April 29, 2005.
05-Oct-2005	[SOUTH AFRICA] Dr. D. R. Lakha: Angioneurotic oedema, dyspnoea, throat toghtness, anxiety, pharyngeal oedema, pruritus, anxiety, pharyngeal oedema, pruritus, flushing, swelling face, swollen tongue; Follow-up#1.
06-Oct-2005	Protocol 2343, Amendment 2.
07-Oct-2005	TELECON FROM FDA expressing Agency concerns with the design of Study 2334 submitted on September 2, 2005, serial no. 141, and recommending that the concerns be addressed via a protocol amendment.
12-Oct-2005	[JAPAN] Munechika Noguchi: Erythema.
17-Oct-2005	TELECON WITH FDA clarifying the timing of the BE trial (Study 2343) submission to the NDA.
25-Oct-2005	New investigators, Protocol C2201: R.A.Levy, T.C.Fagan, J.K.Conrow. Protocol 2310: J.T.Wright. Protocol 2318: N.K.Hollenberg. Protocol 2327: J.R.Mitchell. Protocol 2328: B.C.Lubin, B.C.Pogue, D.A.Sica, R.A.Levy, J.N.Herrod, L.G.Padget, J.Mitchell, J.Soufer, D.M.Benson, G.M.Burgess, K.A.Morris, L.A.Lohrbauer, R.J.Lockwood, M.Fredrick, E.D.Pampe, G.Tannoury. Protocol 2331: H.J.Simon, E.Spierings, R.D.Ward, D.Thompson, A.Barreto, S.B.Jones, S.E.Southworth, D.C.McCluskey.
25-Oct-2005	TELECON WITH FDA discussing review of the final protocol 2343, Amendment 1, serial no. 155 and Amendment 2, serial no. 162. FDA found all submissions acceptable.
25-Oct-2005	E MAIL to/from FDA seeking and receiving guidance on the electronic data required for ECGs in the upcoming NDA for aliskiren.
31-Oct-2005	[DENMARK] Dr. Torben Sandager: Angioneurotic oedema, face oedema, stridor, pruritus; Follow-up#3.
02-Nov-2005	[JAPAN] Munechika Noguchi: Erythema multiforme, stomatitis, neuropathy peripheral, erythema; Follow-up#1.
02-Nov-2005	Summary and assessment of a toxicology report entitled, "Unexpected/new adverse findings during a 104-week oral (feed admixture) carcinogenicity study in rats".
15-Nov-2005	TELECON WITH FDA to receive FDA perspective on risk management plans for new chemical entities. FDA responded that aliskiren does not require a specific risk management plan.

16-Nov-2005	TELECON WITH FDA discussing the aliskiren container labeling. The Division agreed to receive the labeling within 4 months (120 days) of the original NDA submission.
17-Nov-2005	Protocol 2318, Amendment no. 1.
22-Nov-2005	Request for FDA evaluation of the proposed tradename "RASILEZ" for aliskiren. Although the latter is Novartis' preferred tradename, included also is an alternate tradename "TEKTURNA" for FDA consideration. Novartis is planning to submit the NDA in the first quarter of 2006. The trademark report for the proposed tradenames prepared by Medical Error Recognition and Revision Strategies INC. is included.
08-Dec-2005	E MAIL from FDA Dr. Marciniak's summary and comments regarding the aliskiren NDA.
14-Dec-2005	Letter acknowledging an agreement reached between Novartis and the Division thah a Risk Managmenet Plan is not a required componenet of the aliskiren NDA.
14-Dec-2005	New investigators, Protocol C2201: D.Martinez. Protocol 2327: D.D.Schocken, F.H.Messerli, W.Berger. Protocol 2328: P.D.Toth, J.C.Malachowski, P.Rama, S.Michael, T.Isakov, D.Bolshoun, J.T.Forsythe, A.B.Pitterman, Protocol 2331: M.McCartney, M.WIlson, H.J.Downey, M.Lasala, G.V.Figueredo-Cardenas, H.Lui, M.Chen, M.Koren, M.Tonkton, M.Cox, M.Terplan, J.Lehmann, A.Taylor, J.Mitchell, G.Burns.
14-Dec-2005	[Japan] O.Miho. Malignant neoplasm progression, rectal cancer, melaena, anaemia.
14-Dec-2005	[Japan] M.Noguchi. Erythema multiforme, stomatitis, erythema, aphthous stomatitis, dysphagia, pruritus, rash scaly, mucosal erosion, drug eruption. Follow-up # 2.
20-Dec-2005	New investigators, Protocol C2201: N.J.Bohannon, M.D.Shepherd. Protocol 2327: J.M.Neutel. Protocol 2328: G.P.Samraj, A.A.Taylor, M.K.Radbill. Protocol 2331: J.Hsia, E.A.Barranco, A.Hudnut, P.Bachan, M.R.Bishop.
21-Dec-2005	Updated Investigators' Brochure, Edition 5, dated December 12, 2005.
21-Dec-2005	[Japan] O.Miho. Malignant neoplams progression, rectal cancer, melaena, anaemia, rectal haemorrhage. Follow-up # 1.
29-Dec-2005	[Japan] O.Miho. Malignant neoplam progression, rectal cancer, melaena, anaemia, rectal haemorrhage. Follow-up # 2.
09-Jan-2006	FDA FAX containing clinical pharmacology and biopharmaceutics comments on the October 3, 2005 submission serial no. 157.
10-Jan-2006	New Protocol 2222: "An open label, multiple dose study to investigate the pharmacokinetic drug-drug interaction between aliskiren and pioglitazone in healthy volunteers".
12-Jan-2006	New investigator, Protocol 2328: D.Barbaria.
25-Jan-2006	New Protocol 2233, "An open-label, multiple-dose study to evaluate the pharmacokinetics, safety and tolerability of SPP100 (Aliskiren) and Fenofibrate administered alone and in combination in healthy subjects".
07-Feb-2006	[Japan] O.Miho. Malignant neoplam progression, rectal cancer, melaena, anaemia, rectal haemorrhage. Follow-up # 3.
08-Feb-2006	New investigators, Protocol 2327: D.K.Hammett, L.E.Morales. Protocol 2328: L.Dworkin. Protocol 2331: D.Kraus, M.Faulkner.
09-Feb-2006	[Japan] Erythema multiforme, stomatitis, erythema,

	aphthous stomatitis, dysphagia, pruritus, skin exfoliation, mucosal erosion, drug eruption. Follow-up # 2.
10-Feb-2006	New Protocol CSPP100A2232 and administrative amendment 1, "An open label, multiple dose study to investigate the pharmacokinetic drug drug interaction between aliskiren and allopurinol in healthy volunteers".
13-Feb-2006	New investigators, Protocol C2201: R.F.Arakaki, J.C.deSouza. Protocol 2222: M.A.Zinny. Protocol 2233: A.L.Laurent. 2327: F.Thomas, D.L.Rasor, S.G.Chrysant, D.R.Colan, S.Mediratta, H.Gillum, L.E.Mansfield, J.B.Eberly, M.L.Look, D.M.Brandon. Protocol 2328: N.Winer.
14-Feb-2006	Letter describing the rationale for conducting plasma aliskiren concentration assessments in Study 2318, serial no. 157, submitted in response to FDA fax dated January 9, 2006.
16-Feb-2006	Study CSPP100A2304, Amendment 1. Study CSPP100A2305, Amendment 2. Study CSPP1ooA2307, Amendment 1. Study CSPP100A2309, Amendment 1. CSPP100A2327, Amendments 1 and 2.
21-Feb-2006	[Japan] Malignant neoplam progression, rectal cancer, melaena, anaemia, rectal haemorrhage. Follow-up # 4.
14-Mar-2006	PHHO2005JP19032; follow-up (PS)
17-Mar-2006	New Protocol CSPP100A2344.
17-Mar-2006	Studies 2201, 2232, 2310, 2327, 2328, 2331 new investigator.
05-Apr-2006	New investigators to Protocols CSPP100C2201, CSPP100A 2310, CSPP100A2327, CSPP100A2328, CSPP100A2331.
02-May-2006	Provided Investigator's Brochure, Edition 6 and summary of changes.
05-May-2006	New investigators to Studies 2201, 2310, 2327, 2331.
17-May-2006	Provided Investigator's Brochure, Edition 7 and summary of changes. (PS)
26-May-2006	Provided updated comparator and placebo documents to support the following study drugs, which will be used in an upcoming clinical trial; Ramipril 5mg hard gelatin capsule, 6001544.001; Ramipril 10mg hard gelatin capsule, 6001543.001; Irbesartan 150mg hard gelatin capsule, 3768868.003; Placebo to match SPP100 150mg, 6000975.013. (PS)
05-Jun-2006	PHHO2006FR08075 (PS)
08-Jun-2006	PHHO2006FR08075; follow-up. (PS)
20-Jun-2006	New Investigators for Protocol 2310, 2327, 2328, and 2331. (PS)
20-Jun-2006	New Investigators to studies CSPP100C2201, CSPP100A2310, and CSPP100A2328. (PS)
13-Jul-2006	Request for a End of Phase II meeting in order to obtain Agency feedback on a development program to support approval of an aliskiren/amlodipine fixed combination product (PS).
18-Jul-2006	New investigator and change in Form FDA 1572 to Study CSPP100A2201, CSPP100A2331 (PS)
18-Jul-2006	PHHO2005JP19032 Follow-Up.
25-Jul-2006	Amendments No. 1 and 2 to Protocol CSPP100A2103 (PS)
02-Aug-2006	New protocol CSPP100A2105 entitled, "An open label exploratory study to determine the concentration of aliskiren in feces, rectal mucosal biopsy specimens, and plasma, at ptasma steady state after daily oral administration of 300mg in healthy volunteers". (PS)
10-Aug-2006	New investigators to Study No. 2103. New investigator to Study No. 2310 and 2331 (PS)
15-Aug-2006	New Protocol CSPP100A2239 entitled, "A double-blind, double dummy, randomized parallel design trial to

	evaluate the effects of 12 weeks of treatment with 300 mg Aliskiren compared to 5 mg Amlodipine on insulin resistance and endothelial dysfunction in hypertensive patients with metabolic syndrome" (PS)
23-Aug-2006	FDA LETTER responding to the November 22, 2005, correspondence containing tradename proposal (PS)
29-Aug-2006	PHHO2006TR04952 (PS)
01-Sep-2006	PHHO2006TR04952; follow-up (PS)
15-Sep-2006	New investigator to Study No. SPP100A2105, SPP100A2310, SPP100A2327 and SPP100A2331 (PS)
15-Sep-2006	PHHO2006TR04952; Follow-up (PS)
21-Sep-2006	New investigator to Study No. 2103, 2327 and 2328. New investigators to Study No. 2344 (PS)
21-Sep-2006	New Protocol CSPV100A2301 entitled: "A 54-week, open-label, muiticenter study to assess the long-term safety and tolerability of the combination of aliskiren 300mg/ valsartan 320 mg in patients with essential hypertension". New investigators and Amendment No. 1 to Study CSPV100A2301 (PS)
18-Oct-2006	New investigators to Study No. CSPP100A2344 (PS)
19-Oct-2006	New Protocol CSPA100A2301 entitled: "A 54-week, open-label, multicenter study to assess the long-term safety and tolerability of the combination of aliskiren 300 mg/ amlodipine 10 mg in patients with essential hypertension" . New investigators to Study No. CSPA100A2301 (PS)
19-Oct-2006	This Annual Report covers the period August 22, 2005 through August 21, 2006 (PS)
24-Oct-2006	New investigators to Study No. CSPV100A2301 (PS)
31-Oct-2006	PHHO2005JP19032; follow-up (PS)
02-Nov-2006	New investigators to Study No. CSPP100A2344 (PS)
03-Nov-2006	PHHO2006US17925 (PS)
06-Nov-2006	PHHO2006FR08075; Follow-Up (PS)
09-Nov-2006	PHHO2006US17925; follow-up (PS)
17-Nov-2006	New investigators to Study No. CSPV100A2301 (PS)
20-Nov-2006	New investigators to Study No. CSPA100A2301 (PS)
29-Nov-2006	New investigator to Study 2310 and new investigators to Study 2344 (PS)
30-Nov-2006	Request for special protocol assessment for Study CSPP100E2337 (PS)
05-Dec-2006	New investigator/Changes in form 1572 to Study CSPP100A2344 (PS)
05-Dec-2006	Request for special protocol assessment for Study SPP100D2335 (PS)
08-Dec-2006	New Protocol 2340 entitled: "A 36-week, multicenter, randomized, double-blind, placebo controlled, parallel-group study to evaluate the efficacy and safety of aliskiren on the prevention of left ventricular remodeling in high risk post-acute myocardial infarction patients when added to optimized standard therapy" (PS)
08-Dec-2006	FDA LETTER acknowledging recipr of the November 30, 2006, serial number 226, request for a special clinical protocol assessment.
14-Dec-2006	New investigators to Study CSPA100A2301 (PS)
15-Dec-2006	New investigators to Study CSPV100A2301 (PS)
19-Dec-2006	New CRO for Study 2103 (PS)
21-Dec-2006	New investigators to Study SPP100A2310, new investigator to Study SPP100A2344 and various changes in Form FDA 1572 (PS))
21-Dec-2006	New investigators to Study CSPP100A2344 (PS)
21-Dec-2006	New Protocol CSPP100AUS02 entitled: "A randomized, open-label, blinded endpoint, multi-center, cross-over study to evaluate the effect of high and low sodium

	diets on reduction in mean 24-hour ambulatory blood pressure in systolic hypertensive patients treated with aliskiren (300 mg)" (PS)
10-Jan-2007	At this time, Novartis is providing an Information Amendment to provide updated Chemistry, Manufacturing and Controls Information for the following drug products in support of upcoming clinical trials, SPP100 75 mg (alsikiren) Tablets, 3764313.011 and SPP100 150 mg (aisikiren) Tablets, 3765070.012 (PS)
12-Jan-2007	New investigators and changes for FDA form 1571 to Study CSPP100AUS02 and new investigator to Study CSPP100A2344 (PS)
17-Jan-2007	FDA LETTER responding to the November 30, 2006 request, serial number 226 for a special protocol assessment.
30-Jan-2007	Email from FDA containing statistical comments on the December 8, 2006, serial number 229.
02-Feb-2007	New investigators to Study CSPP100AUS02, CSPP100A2340 and CSPP100A2344. Changes in FDA Form 1571 to Study CSPP100A2201, CSPP100A2310 and CSPP100A2344 (PS)
06-Feb-2007	New investigators to Study CSPA100A2301 (PS)
19-Feb-2007	Novartis is providing a CMC information amendment to provide updated information for the following drug products in support of upcoming clinical trials, SPP100 150 mg (alsikiren) Tablets, 3765070.017 (PS)
27-Feb-2007	New investigator to Study CSPP100AUS02 and CSPP100A2340 and various changes in Form FDA 1572 to Study CSPA100A2301, CSPP100A2340 and CSPP100A2344 (PS)
27-Feb-2007	This correspondence to the FDA is to acknowledge agreement with the recommendations contained in the FDA response document, as well as obtain FDA feedback on a few items and to gain clarification of the requirements to obtain an albuminuria indication (PS)

NDA PERIOD

10-Feb-2006	Original new drug application for the treatment of hypertension, alone and in combination with other antihypertensive agents. Submitted in electronic format on 1 DLT.
23-Feb-2006	FDA FAX containing comments and request for information regarding SAE reports.
27-Feb-2006	TELECON WITH FDA responding to a faxed request for additional information on SAE reports to facilitate review of the NDA.
28-Feb-2006	In response to the request on February 27, 2006 from Dr. Marciniak in regards to more details on SAEs and term listings for adverse events (ES).
08-Mar-2006	FDA LETTER acknowledging the February 10, 2006 new IND 21-985 for Rasilez, providing for the treatment of hypertension, alone and in combination with other antihypertensive agents.
10-Mar-2006	TELECON concerning Rasilez NDA Request for information: Study Titles and locaton of specification and methods in the NDA.
10-Mar-2006	TELECON concerning Rasilez NDA Request for Information: Additional PK annotations needed for annotated Rasilez package insert. Lydia Velazquez contacted Kimberly Dickerson via voicemail to request that updated annotations to the Razilez package insert be provided to facilitate the Rasilez NDA review.
13-Mar-2006	Response to FDA providing additional details on SAEs and term listings for adverse events.
14-Mar-2006	As requested and in order to facilitate review of the NDA, provided document containing study numbers and titles of trials included in the NDA,
14-Mar-2006	Email to FDA responding to FDA request for additional information to facilitate the NDA review, which includes a document that contains the study numbers and titles of trials included in the NDA. This submission is being submitted formally to the FDA as well (ES)
17-Mar-2006	Response to FDA providing additional information related to the serious adverse events cited in the NDA.
17-Mar-2006	Email responding to the FDA request for electronic tumor datasets (ES)
20-Mar-2006	Response to FDA request that the PK section of the label be annotated to the summary documents of the submission rather than solely to the study number (ES).
24-Mar-2006	TELECON concerning Rasilez NDA Request for Information: Biopharmaceutics and Clinical Pharmacology (ES).
27-Mar-2006	Email to FDA responding to tho the request for Biopharm & Clin Pharm Review Aids. This submission will be formally submitted to FDA as well (ES)
31-Mar-2006	Provided additional information to assist FDA with the navigation and review of NDA 21-985.
03-Apr-2006	In accordance with previous agreement, provided an additional study report to assist with the review of the NDA.
04-Apr-2006	As agreed during a recent discussion with FDA, provided additional information to assist the Agency with the review of NDA 21-985.

05-Apr-2006	Additional information to aid review and navigation of the NDA, submitted in response to a request from the clinical pharmacologist and the biopharmaceutist.
07-Apr-2006	Email from FDA regarding an updated TOC item 6 and the status of the PK studies 2101, 2212, 2230, 2235 and 2318 (ES)
07-Apr-2006	Email from FDA containing a summary of unresolved issues pertaining to the NDA (ES)
07-Apr-2006	Email from FDA pertaining to the BE study 2343 and the missing raw data (ES)
07-Apr-2006	Email from FDA responding to answers given by Novartis to FDA questions pertaining to the submission ready appendices for updated PI annotations, gender & race statistics, navigation aids and dissolution raw data (ES)
07-Apr-2006	Email from FDA responding to Novartis' responses to FDA questions pertaining to the development report for dissolution and specs, 300mg in multi-media (ES)
11-Apr-2006	Email to FDA resending email which was previously sent on April 10, which responded to concerns cited by Dr. Velazquez.
11-Apr-2006	Email from FDA with comments on unresolved issues.
11-Apr-2006	Email response to FDA on the Raw data and analytical report for Study 2343.
12-Apr-2006	Email response to FDA request on April 11, 2006 for CMC and Human Pharmacology Bioavailability/Bioequivalence information (ES)
12-Apr-2006	Email response from FDA regarding information sent in response to concerns cited by Dr. Velazquez.
19-Apr-2006	Response provided to the Division in response to Agency questions conveyed in a March 22, 2006 contact related to the NDA.
19-Apr-2006	As agreed with the Regulatory Project Manager and the Clinical Pharmacologist and Biopharmaceutist, provided additional information to assist with the review of the NDA.
24-Apr-2006	FDA LETTER stating that the NDA application is sufficiently complete to permit a substantive review. Reference is also made to submissions dated March 13, 14, 17, 31 and April 3, 4, and 5, 2006.
27-Apr-2006	Response to request for information by Division of Scientific Investigations (PS)
02-May-2006	Response to FDA nonclinical reviewer request of April 21, 2006.
24-May-2006	TELECON with FDA to discuss CMC information request. He was reviewing the drug substanoe documents discussion stereochemistry and would find it helpful if Novartis could provide a narrative description of the stereochemistry for each synthesis step. Justification should be provided to support statements. An example was given where we present a discussion of potential sterio-isomers giving the statement that "16 are theoretically possible. In practice, 6 stereo-isomers are possible from the synthetic route
12-Jun-2006	Email from FDA requesting information on the location in the NDA of the CRF and narrative of a patient in Study 2203 (ES)
13-Jun-2006	120-Day Safety Update for Original Application of February 13, 2006. (ES)
16-Jun-2006	Email from the FDA requesting information on the CRF submission in the NDA, the CRFs and all other available clinical documentation for subgroups of

	patients and the status of Study 2327 (ES)
22-Jun-2006	Response to FDA Request dated June 12, 2006 for additional Clinical Information. (ES)
26-Jun-2006	TELECON concerning Rasilez Pre-Clinical 13 week mechanistic study (ES).
27-Jun-2006	Provided, in response to FDA request, additional nonclinical pharmacology/toxicology information. (ES)
28-Jun-2006	Amendment to pending application. This submission provides for a proposed patient package insert (PPI) for Rasilez. (ES)
05-Jul-2006	On 24-May-2006, Xaviar Ysern, the assigned Chemistry Reviewer, contacted Novartis to request additional information on the stereochemistry of the drug substance. This requested information was faxed to Mr. Ysern on 09-Jun-2006 and is provided now as an official amendment to the NDA No. 21-985. (ES)
06-Jul-2006	Reference is made to the June 16, 2006 correspondence from Mr, John David, Regulatory Health Project Manager, requesting that Novartis provide additional information related to NDA 21-985. This contains the response document. (ES)
11-Jul-2006	This submission contains a proposal for the data to be submitted in support of a second manufacturing site with an approximate timeline for amending the application
25-Jul-2006	FDA LETTER comments on the July 6, 2006 submission, containing answers to questions from the "Response to Health Authority Questions" (ES)
01-Aug-2006	Reference is made to NDA 21-985 for Rasilez_ (aliskiren) tablets, a renin inhibitor currently under review for the treatment of hypertension. Reference is also made to the July 25, 2006 letter from the Division requesting that Novartis provide additional information related to NDA 21-985. In response to the request, we offer the response document enclosed with this correspondence. (ES)
14-Aug-2006	In response to FDA request of June 16, 2006 and July 25, 2006, provided is the requested additional information (ES)
16-Aug-2006	In response to FDA request of June 15, 2006 and July 25, 2006, provided is the response document (ES)
16-Aug-2006	FDA LETTER rsponding to correspondence submitted on July 11, 2006 for an amendment of the NDA for a new drug product manufacturing site (ES)
17-Aug-2006	Email from FDA requesting additional information on the tumor which is referenced in the study report, page #35 of 1772, 4th para (ES)
23-Aug-2006	FDA LETTER responding to the November 22, 2005, correspondence containing tradename proposal (ES)
23-Aug-2006	FDA LETTER comments on the August 16, 2006, submission, containing answers to questions from the "Response to HA Questions" dated August 15, 2006 (ES)
31-Aug-2006	Response to FDA request on August 17, 2006 regarding the NDA (ES)
15-Sep-2006	In response to FDA request of September 7, 2006, provided is a response document to the FDA questions (ES)
26-Sep-2006	This submission is in response to FDA request of September 5, 2006 with questions related to the NDA (ES)
28-Sep-2006	This submission is in response to the August 23, 2006 correspondence from the FDA agreeing to review results related to Study 2327 without resetting the

	PDUFA deadline (ES)
04-Oct-2006	This submission is in response to the FDA request of September 7, 2006 and September 22, 2006 with questions related to the NDA (ES)
05-Oct-2006	This submission is being submitted in response to the FDA request of September 22, 2006 for a limited safety update (ES)
06-Oct-2006	This submission is in response to the FDA request from the Cardio-Renal Division for safety related data and clarification on items previously submitted (ES)
10-Oct-2006	Telephone Report
13-Oct-2006	This submission is in response to the FDA request of June 29, 2006 for stability data for batches of drug substance manufactured according to process B (ES)
17-Oct-2006	This submission is in response to the FDA letter dated August 23, 2006 regarding the tradename Tekturna, as well as the August 23, 2006 letter with general comments regarding the carton and container labeling (ES)
23-Oct-2006	Response to FDA request for safety related data and clarification on items previously submitted (ES)
23-Oct-2006	Response to FDA request on October 10, 2006 for a narrative discussion of critical process parameters identified for the manufacture of the drug product (ES)
25-Oct-2006	Response to FDA request of September 22, 2006 for a limited safety update (ES)
26-Oct-2006	In response to the FDA request on October 17, 2006 for an explanation of the mechanism of action of Tekturna (ES)
27-Oct-2006	FDA LETTER requesting additional information on the CMC section of the NDA.
02-Nov-2006	Response to FDA CMC request letter dated October 27, 2006 (ES)
02-Nov-2006	TELECON with the FDA on October 27, 2006 to clarify the FDA's previous request for eCRFs of elevated CK.
03-Nov-2006	In response, this submission provides the proposed package insert, annotated package insert, and proposed patient package insert (PPI) for Tekturna (ES)
03-Nov-2006	In response to FDA request on October 27, 2006 with a clarification to the request for eCRFs of elevated CK (ES)
04-Nov-2006	In response to the prior agreement between Novartis and the Cardio-Renal Division to provide additional information to the Tekturna NDA. In accordance with that basic agreement, the requested information is enclosed with this correspondence (ES)
07-Nov-2006	In response to the FDA request and as part of the ongoing monitoring of the gastrointestinal safety of aliskiren (ES)
09-Nov-2006	Response to FDA request for a status update on the proposed pediatric study request. Novartis is requesting that the Division review the appended PPSR for Tekturna tablets, which will provide guidance for the use of aliskiren to reduce blood pressure of pediatric patients 6-17 years of age The data will be derived from clinical pharmacology data and phase 3 efficacy and safety data (ES)
15-Nov-2006	In response to the FDA request regarding the dose response curve for aliskiren monotherapy, included is the appended meta-analysis of clinical data obtained from all placebo-controlled trials (ES)

16-Nov-2006	In response to FDA request letter dated October 27, 2006 and the request on November 8, 2006 concerning the proposed dissolution method (ES)
17-Nov-2006	This submission is in response to the FDA statistical question on November 9, 2006 (ES)
21-Nov-2006	Respnse to FDA request on November 20, 2006 with a statistical question (ES)
24-Nov-2006	FDA minutes of the November 13, 2006, Novartis/FDA Type C meeting to discuss the CMC IR letter.
29-Nov-2006	Response to FDA request regarding product protection from moisture during dispensing, during the November 27, 2006 teleconference (ES)
30-Nov-2006	In response to the FDA concern during the November 27, 2006 teleconference, as to whether the starting dose recommendations for the general population are appropriate for the elderly popoulation (ES)
01-Dec-2006	The submission contains summaries which include supplementary analyses and plots elaborating on the use of Tekturna in elderly patients, and an integrated summary of Novartis_ position on the gastrointestinal safety of the compound which were discussed at the November 27, 2006 teleconference (ES).
04-Dec-2006	In response to the prior agreement between Novartis and the Cardio-Renal Division to provide additional information to the Tekturna NDA. In accordance with that basic agreement, the requested information is enclosed with this correspondence. Please note desk copies of this submission where provided on December 6, 2006 and have been placed in records retention. (ES)
08-Dec-2006	This submission is in response to the FDA request on December 7, 2006 for additional supportive documentation to faciliate the review of the NDA (ES)
08-Dec-2006	FDA LETTER Information request for clinical section of the December 4, 2006 submission.
12-Dec-2006	FDA LETTER informing Novartis that the FDA is extending the goal date by three months to provide time for a full review of the major amendment submitted on December 4, 2006.
14-Dec-2006	In response to the FDA request for additional information (ES)
20-Dec-2006	This submission is in response to the blinding of Study No. SPP100A2103 (HS)
12-Jan-2007	This submission is in response to the FDA request for additional information related to Study No. SPP100A2327 (ES)
16-Jan-2007	FDA LETTER comments on the October 17 and November 3, 2006 submissions containing updated carton and container labeling, proposed package insert, annotated package insert and proposed patient package insert.
26-Jan-2007	This submission contains revised carton and container labels for Tekturna in response to the FDA request dated January 16, 2007 (ES)
16-Feb-2007	Email response to the FDA request dated February 15, 2007 for additional information regarding Study SPP100A2103 (ES)
16-Feb-2007	Fax from FDA containing the 1st draft of the PPI
26-Feb-2007	This submission is in response to the FDA request dated February 15, 2007 for additional information regarding Study SPP100A2103 (ES)
26-Feb-2007	This submission is in response to the FDA recent labeling comments (ES)

27-Feb-2007	This submission is in response to the FDA request for additional information related to Study SPP100A2327 (ES)
27-Feb-2007	This correspondence is in response to the FDA's recent labeling feedback. Novartis is providing documents which accepts all of the FDA's entries as black print and shows Novartis' revisions in color (ES)
28-Feb-2007	This correspondence is in response to the FDA's recent feedback regarding the Phase 4 commitments (ES)
02-Mar-2007	Fax to FDA containing the email sent regarding the postmarketing study commitments (ES)
05-Mar-2007	FDA LETTER approval of the NDA. This new drug application provides for the use of Tekturna (aliskiren) 150 mg and 300 mg Tablets for the treatment of hypertension.
06-Mar-2007	WWW, TKT-WS-0110-A Tekturna Website Creative. WWW, TKT-WS-0110-B Tekturna Website Manuscript
09-Mar-2007	Draft professional and consumer promotional materials submitted to DDMAC for review (ES)